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APPLICATION FOR UNITED STATES LETTERS PATENT

INVENTORS: Solomon Ungashe
Wei Zheng
J. J. Wright
Andrew Pennell
Brett Premack
Thomas Schall

TITLE: BIS-ARYL SULFONAMIDES

ATTORNEY: Shannon Mrksich
Reg. No. 36,675

BRINKS HOFER GILSON & LIONE
P.O. BOX 10395
CHICAGO, ILLINOIS 60610
(312) 321-4200

BIS-ARYL SULFONAMIDES

RELATED APPLICATIONS

[0001] This application claims priority to U.S. provisional application Serial No. 60/427,670 filed November 18, 2002. The disclosure of the priority application is incorporated by reference herein in its entirety.

BACKGROUND OF THE INVENTION

[0002] The present invention provides compounds, pharmaceutical compositions containing one or more of those compounds or their pharmaceutically acceptable salts, which are effective in inhibiting the binding or function of various chemokines to receptors, such the chemokine TECK to the CCR9 receptor. As antagonists or modulators for the CCR9 receptor, the compounds and compositions have utility in treating inflammatory and immune disorder conditions and diseases.

[0003] Chemokines are chemotactic cytokines that are released by a wide variety of cells and attract various types of immune system cells, such as macrophages, T cells, eosinophils, basophils and neutrophils, to sites of inflammation (reviewed in Schall, *Cytokine*, 3:165-183 (1991), Schall, *et al.*, *Curr. Opin. Immunol.*, 6:865 873 (1994) and Murphy, *Rev. Immun.*, 12:593-633 (1994)). In addition to stimulating chemotaxis, other changes can be selectively induced by chemokines in responsive cells, including changes in cell shape, transient rises in the concentration of intracellular free calcium ions ($[Ca^{2+}]$), granule exocytosis, integrin up-regulation, formation of bioactive lipids (*e.g.*, leukotrienes) and respiratory burst, associated with leukocyte activation. Thus, the chemokines are early triggers of the inflammatory response, causing inflammatory mediator release, chemotaxis and extravasation to sites of infection or inflammation.

[0004] T lymphocyte (T cell) infiltration into the small intestine and colon has been linked to the pathogenesis of coeliac diseases, food allergies, rheumatoid arthritis, human inflammatory bowel diseases (IBD)

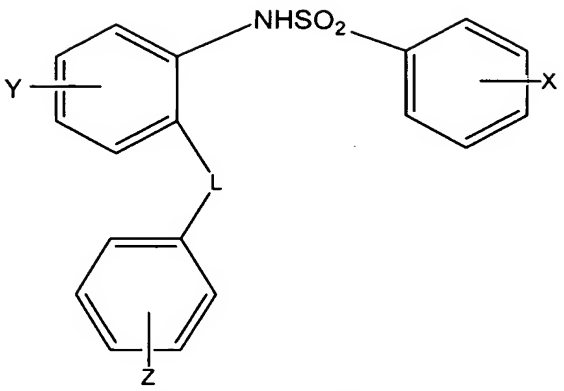
which include Crohn's disease and ulcerative colitis. Blocking trafficking of relevant T cell populations to the intestine can lead to an effective approach to treat human IBD. More recently, chemokine receptor 9 (CCR9) has been noted to be expressed on gut-homing T cells in peripheral blood, elevated in patients with small bowel inflammation such as Crohn's disease and celiac disease. The only CCR9 ligand identified to date, TECK (thymus-expressed chemokine) is expressed in the small intestine and the ligand receptor pair is now thought to play a pivotal role in the development of IBD. In particular, this pair mediates the migration of disease causing T cells to the intestine. See for example, Zaballos, *et al.*, *J. Immunol.*, 162(10):5671-5675 (1999); Kunkel, *et al.*, *J. Exp. Med.* 192(5):761-768 (2000); Papadakis, *et al.*, *J. Immunol.*, 165(9):5069-5076 (2000); Papadakis, *et al.*, *Gastroenterology*, 121(2):246-254 (2001); Campbell, *et al.*, *J. Exp. Med.*, 195(1):135-141 (2002); Wurbel, *et al.*, *Blood*, 98(9):2626-2632 (2001); and Uehara, *et al.*, *J. Immunol*, 168(6):2811-2819 (2002).

[0005] Compounds that modulate the function of chemokine receptors are attractive as therapeutic agents for the treatment of inflammatory and other conditions and diseases associated with chemokine receptor activation.

BRIEF SUMMARY OF THE INVENTION

[0006] The present invention is directed to compounds and pharmaceutically acceptable salts thereof, compositions, and methods useful in modulating chemokine activity. The compounds and salts thereof, compositions, and methods described herein are particularly useful in modulating CCR9 chemokine activity.

[0007] In one embodiment, the modulators of the present invention are of the formula (I):



where X, Y and Z are as defined below. Salts of these compounds are also within the scope of the invention.

[0008] In another aspect, the present invention provides compositions useful in modulating chemokine activity. In one embodiment, a composition according to the present invention comprises a modulator according to the invention and a pharmaceutically acceptable carrier or excipient.

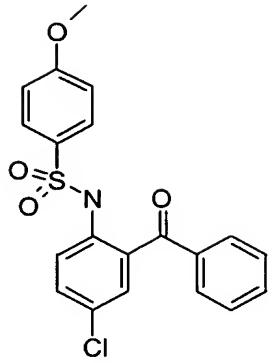
[0009] In yet another aspect, the present invention provides a method of modulating chemokine function in a cell, comprising contacting the cell with a therapeutically effective amount of a modulator or composition according to the invention.

[0010] In still another aspect, the present invention provides a method for treating a chemokine-mediated condition or disease, comprising administering to a subject a safe and effective amount of a modulator or composition according to the invention.

[0011] In addition to the compounds provided herein, the present invention further provides pharmaceutical compositions containing one or more of these compounds, as well as methods for the use of these compounds in therapeutic methods, primarily to treat diseases associated with CCR9 signaling activity.

BRIEF DESCRIPTION OF THE FIGURE

[0012] FIG. 1 is a graph showing *in vivo* efficacy for the known compound tested in Example 40. Closed triangle: vehicle; Open circle: CCR9 antagonist of the formula:



DETAILED DESCRIPTION OF THE INVENTION

General

[0013] The present invention is directed to compounds and salts thereof, compositions and methods useful in the modulation of chemokine receptor function, particularly CCR9 function. Modulation of chemokine receptor activity, as used herein in its various forms, is intended to encompass antagonism, agonism, partial antagonism, inverse agonism and/or partial agonism of the activity associated with a particular chemokine receptor, preferably the CCR9 receptor. Accordingly, the compounds of the present invention are compounds which modulate at least one function or characteristic of mammalian CCR9, for example, a human CCR9 protein. The ability of a compound to modulate the function of CCR9, can be demonstrated in a binding assay (*e.g.*, ligand binding or agonist binding), a migration assay, a signaling assay (*e.g.*, activation of a mammalian G protein, induction of rapid and transient increase in the concentration of cytosolic free calcium), and/or cellular response assay (*e.g.*, stimulation of chemotaxis, exocytosis or inflammatory mediator release by leukocytes).

Abbreviations and Definitions

[0014] When describing the compounds, compositions, methods and processes of this invention, the following terms have the following meanings, unless otherwise indicated.

[0015] When describing the compounds, compositions, methods and processes of this invention, the following terms have the following meanings, unless otherwise indicated.

[0016] "Alkyl" by itself or as part of another substituent refers to a hydrocarbon group which may be linear, cyclic, or branched or a combination thereof having the number of carbon atoms designated (i.e., C_{1-8} means one to eight carbon atoms). Examples of alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, cyclohexyl, cyclopentyl, (cyclohexyl)methyl, cyclopropylmethyl and the like. Examples of substituted alkyl include haloalkyl, thioalkyl, aminoalkyl, and the like.

[0017] "Cycloalkyl" refers to hydrocarbon rings having the indicated number of ring atoms (e.g., C_{3-6}cycloalkyl) and being fully saturated or having no more than one double bond between ring vertices. "Cycloalkyl" is also meant to refer to bicyclic and polycyclic hydrocarbon rings such as, for example, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, etc.

[0018] "Alkylene" by itself or as part of another substituent means a divalent radical derived from an alkane, as exemplified by -$CH_2CH_2CH_2CH_2$-. Typically, alkyl (or alkylene) groups having 8 or fewer carbon atoms are preferred in the present invention.

[0019] "Alkenyl" refers to an unsaturated hydrocarbon group which may be linear, cyclic or branched or a combination thereof. Alkenyl groups with 2-8 carbon atoms are preferred. The alkenyl group may contain 1, 2 or 3 carbon-carbon double bonds. Examples of alkenyl groups include ethenyl, n-propenyl, isopropenyl, n-but-2-enyl, n-hex-3-enyl and the like.

[0020] "Alkoxy" and "alkylthio" (or thioalkoxy) are used in their conventional sense and refer to an alkyl groups attached to the remainder of the molecule via an oxygen atom or a sulfur atom, respectively. Examples of alkoxy and thioalkoxy include methoxy, ethoxy, isopropoxy, butoxy, cyclopentyloxy, thiomethoxy, and the like.

[0021] "Alkynyl" refers to an unsaturated hydrocarbon group which may be linear, cyclic or branched or a combination thereof. Alkynyl groups with 2-8 carbon atoms are preferred. The alkynyl group may contain

1, 2 or 3 carbon-carbon triple bonds. Examples of alkynyl groups include ethynyl, n-propynyl, n-but-2-ynyl, n-hex-3-ynyl and the like.

[0022] "Aryl" refers to a polyunsaturated, aromatic hydrocarbon group having a single ring or multiple rings which are fused together or linked covalently. Aryl groups with 6-10 carbon atoms are preferred. Examples of aryl groups include phenyl and naphthalene-1-yl, naphthalene-2-yl, biphenyl and the like.

[0023] "Halo" or "halogen", by itself or as part of a substituent refers to a chlorine, bromine, iodine, or fluorine atom. Additionally, "haloalkyl" refers to a monohaloalkyl or polyhaloalkyl group, most typically substituted with from 1-3 halogen atoms. Examples include 1-chloroethyl, 3-bromopropyl, trifluoromethyl and the like.

[0024] "Heterocyclyl" refers to a saturated or unsaturated non-aromatic group containing at least one heteroatom. "Heteroaryl" refers to an aromatic group containing at least one heteroatom. Each heterocyclyl and heteroaryl can be attached at any available ring carbon or heteroatom. Each heterocyclyl and heteroaryl may have one or more rings. When multiple rings are present, they can be fused together or linked covalently. Each heterocyclyl and heteroaryl must contain at least one heteroatom (typically 1 to 5 heteroatoms) selected from nitrogen, oxygen or sulfur. Preferably, these groups contain 0-3 nitrogen atoms, 0-1 sulfur atoms and 0-1 oxygen atoms. Examples of saturated and unsaturated heterocyclyl groups include pyrrolidine, imidazolidine, pyrazolidine, piperidine, 1,4-dioxane, morpholine, thiomorpholine, piperazine, 3-pyrroline and the like. Examples of unsaturated and aromatic heterocycyl groups include pyrrole, imidazole, thiazole, oxazole, furan, thiophene, triazole, tetrazole, oxadiazole, pyrazole, isoxazole, isothiazole, pyridine, pyrazine, pyridazine, pyrimidine, triazine, indole, benzofuran, benzothiophene, benzimidazole, benzopyrazole, benzthiazole, quinoline, isoquinoline, quinazoline, quinoxaline and the like. Heterocyclyl and heteroaryl groups can be unsubstituted or substituted. For substituted groups, the substitution may be on a carbon or heteroatom. For

example, when the substitution is =O, the resulting group may have either a carbonyl (-C(O)-) or a N-oxide (-N(O)-).

[0025] Suitable substituents for substituted alkyl, substituted alkenyl, substituted alkynyl and substituted cycloalkyl include -halogen, -OR', -NR'R", -SR', -SiR'R"R"', -OC(O)R', -C(O)R', -CO_2R', -CONR'R", -OC(O)NR'R", -NR"C(O)R', -NR'-C(O)NR"R"', -NR"$C(O)_2$R', -S(O)R', -$S(O)_2$R', -$S(O)_2$NR'R", -NR'$S(O)_2$R", -CN, oxo (=O or –O-) and -NO_2 in a number ranging from zero to (2m'+1), where m' is the total number of carbon atoms in such radical.

[0026] Suitable substituents for substituted aryl, substituted heteroaryl and substituted heterocyclyl include -halogen, unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl, unsubstituted or substituted alkynyl, unsubstituted or substituted cycloalkyl, -OR', oxo (=O or -O), -OC(O)R', -NR'R", -SR', -R', -CN, -NO_2, -CO_2R', -CONR'R", -C(O)R', -OC(O)NR'R", -NR"C(O)R', -NR"$C(O)_2$R', -NR'-C(O)NR"R"', -NH-$C(NH_2)$=NH, -NR'$C(NH_2)$=NH, -NH-$C(NH_2)$=NR', -S(O)R', -$S(O)_2$R', -$S(O)_2$NR'R", -NR'$S(O)_2$R" and -N_3 in a number ranging from zero to the total number of open valences on the aromatic ring system.

[0027] As used above, R', R" and R"' each independently refer to a variety of groups including hydrogen, halogen, unsubstituted or substituted C_{1-8} alkyl, unsubstituted or substituted C_{3-6} cycloalkyl, unsubstituted or substituted C_{2-8} alkenyl, unsubstituted or substituted C_{2-8} alkynyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted heterocyclyl. Preferably, R', R" and R"' independently refer to a variety of groups selected from the group consisting of hydrogen, unsubstituted C_{1-8} alkyl, unsubstituted heteroalkyl, unsubstituted aryl, aryl substituted with 1-3 halogens, unsubstituted C_{1-8} alkyl, unsubstituted C_{1-8} alkoxy, unsubstituted C_{1-8} thioalkoxy groups, or unsubstituted aryl-C_{1-4} alkyl groups. When R' and R" are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 3-, 4-, 5-, 6-, or 7-membered ring (for example, -NR'R" includes 1-pyrrolidinyl and 4-morpholinyl).

[0028] Alternatively, two of the substituents on adjacent atoms of the aryl, heteroaryl or heterocycyl ring may optionally be replaced with a substituent of the formula -T-C(O)-$(CH_2)_q$-U-, wherein T and U are independently –NR'-, -O-, -CH_2- or a single bond, and q is an integer of from 0 to 2. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -A-$(CH_2)_r$-B-, wherein A and B are independently -CH_2-, -O-, -NR'-, -S-, -S(O)-, -$S(O)_2$-, -$S(O)_2$NR'- or a single bond, and r is an integer of from 1 to 3. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -$(CH_2)_s$-X-$(CH_2)_t$-, where s and t are independently integers of from 0 to 3, and X is -O-, -NR'-, -S-, -S(O)-, -$S(O)_2$-, or -$S(O)_2$NR'-. The substituent R' in -NR'- and -$S(O)_2$NR'- is selected from hydrogen or unsubstituted C_{1-6} alkyl.

[0029] "Heteroatom" is meant to include oxygen (O), nitrogen (N), sulfur (S) and silicon (Si).

[0030] "Pharmaceutically acceptable" carrier, diluent, or excipient is a carrier, diluent, or excipient compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

[0031] "Pharmaceutically-acceptable salt" refers to a salt which is acceptable for administration to a patient, such as a mammal (e.g., salts having acceptable mammalian safety for a given dosage regime). Such salts can be derived from pharmaceutically-acceptable inorganic or organic bases and from pharmaceutically-acceptable inorganic or organic acids, depending on the particular substituents found on the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Salts derived from pharmaceutically-acceptable inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic, manganous, potassium,

sodium, zinc and the like. Salts derived from pharmaceutically-acceptable organic bases include salts of primary, secondary, tertiary and quaternary amines, including substituted amines, cyclic amines, naturally-occurring amines and the like, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Salts derived from pharmaceutically-acceptable acids include acetic, ascorbic, benzenesulfonic, benzoic, camphosulfonic, citric, ethanesulfonic, fumaric, gluconic, glucoronic, glutamic, hippuric, hydrobromic, hydrochloric, isethionic, lactic, lactobionic, maleic, malic, mandelic, methanesulfonic, mucic, naphthalenesulfonic, nicotinic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic and the like.

[0032] Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, for example, Berge, S.M., et al, "Pharmaceutical Salts", *J. Pharmaceutical Science*, 1977, *66*:1-19). Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[0033] The neutral forms of the compounds may be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but otherwise the salts are equivalent to the parent form of the compound for the purposes of the present invention.

[0034] "Salt thereof" refers to a compound formed when the hydrogen of an acid is replaced by a cation, such as a metal cation or an organic cation and the like. Preferably, the salt is a pharmaceutically-acceptable salt, although this is not required for salts of intermediate compounds which are not intended for administration to a patient.

[0035] In addition to salt forms, the present invention provides compounds which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the present invention. Additionally, prodrugs can be converted to the compounds of the present invention by chemical or biochemical methods in an *ex vivo* environment. For example, prodrugs can be slowly converted to the compounds of the present invention when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent.

[0036] "Therapeutically effective amount" refers to an amount sufficient to effect treatment when administered to a patient in need of treatment.

[0037] "Treating" or "treatment" as used herein refers to the treating or treatment of a disease or medical condition (such as a bacterial infection) in a patient, such as a mammal (particularly a human or a companion animal) which includes:

[0038] ameliorating the disease or medical condition, i.e., eliminating or causing regression of the disease or medical condition in a patient;

[0039] suppressing the disease or medical condition, i.e., slowing or arresting the development of the disease or medical condition in a patient; or

[0040] alleviating the symptoms of the disease or medical condition in a patient.

[0041] Certain compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, both solvated forms and unsolvated forms are intended to be

encompassed within the scope of the present invention. Certain compounds of the present invention may exist in multiple crystalline or amorphous forms (i.e., as polymorphs). In general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention.

[0042] Certain compounds of the present invention possess asymmetric carbon atoms (optical centers) or double bonds; the racemates, diastereomers, geometric isomers and individual isomers (e.g., separate enantiomers) are all intended to be encompassed within the scope of the present invention. The compounds of the present invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^{3}H), iodine-125 (^{125}I) or carbon-14 (^{14}C). All isotopic variations of the compounds of the present invention, whether radioactive or not, are intended to be encompassed within the scope of the present invention.

Compounds that Modulate CCR9 Activity

[0043] The present invention provides compounds that modulate CCR9 activity. Specifically, the invention provides compounds having anti-inflammatory or immunoregulatory activity. The compounds of the invention are thought to interfere with inappropriate T-cell trafficking by specifically modulating or inhibiting a chemokine receptor function. Chemokine receptors are integral membrane proteins which interact with an extracellular ligand, such as a chemokine, and mediate a cellular response to the ligand, *e.g.*, chemotaxis, increased intracellular calcium ion concentration, etc. Therefore, modulation of a chemokine receptor function, *e.g.*, interference with a chemokine receptor ligand interaction, will modulate a chemokine receptor mediated response, and treat or prevent a chemokine receptor mediated condition or disease. Modulation of a chemokine receptor function includes both inducement and inhibition of the function. The type of modulation accomplished will depend on the characteristics of the compound, i.e., antagonist or full, partial or inverse agonist.

[0044] Without intending to be bound by any particular theory, it is believed that the compounds provided herein interfere with the interaction between a chemokine receptor and one or more cognate ligands. In particular, it is believed that the compounds interfere with the interaction between CCR9 and a CCR9 ligand, such as TECK. Compounds contemplated by the invention include, but are not limited to, the exemplary compounds provided herein and salts thereof.

[0045] For example, compounds of this invention act as potent CCR9 antagonists, and this antagonistic activity has been further confirmed in animal testing for inflammation, one of the hallmark disease states for CCR9. Accordingly, the compounds provided herein are useful in pharmaceutical compositions, methods for the treatment of CCR9-mediated diseases, and as controls in assays for the identification of competitive CCR9 antagonists.

CCR9 antagonists as treatments of cancer

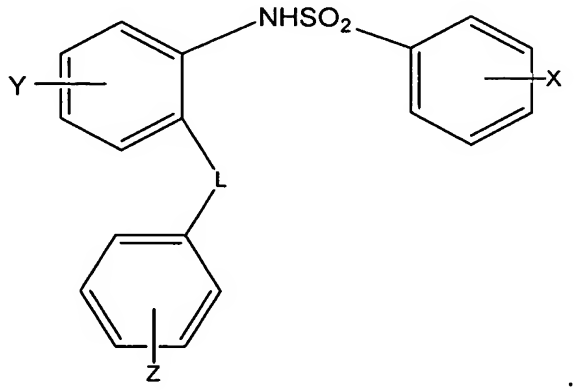
[0046] In additional to inflammatory diseases, cancers that are caused by uncontrolled proliferation of T cells may be treated with a CCR9 antagonist. Certain types of cancer are caused by T cells expressing chemokine receptor CCR9. For example, thymoma and thymic carcinoma are diseases in which cancer cells are found in the tissues of the thymus, an organ where lymphocyte development occurs. T cells in the thymus, called thymocytes, are known to express functional CCR9; its ligand is highly expressed in the thymus. Another example is the acute lymphocytic leukemia (ALL), also called acute lymphoblastic leukemia and acute, is a common leukemia, which can occur in children as well as adults. Recent studies have shown that T cells in patients with ALL selectively express high level of CCR9 (Qiuping Z et al., Cancer Res. 2003, 1;63(19):6469-77)

[0047] Chemokine receptors have been implicated in cancer. Although the exact mechanisms of chemokine receptors' involvements have yet to be full understood, such receptors are known to promote the growth of cancer cells (proliferation), facilitate the spread of cancer cells (metastasis) or help them resist program cell death (apoptosis). For example, CCR9 in a

cancer T cell line MOLT-4 provides the cells with a survival signal, allowing them to resist apoptosis (Youn BS, et al., Apoptosis. 2002 Jun;7(3):271-6). In the cases of thymoma, thymic carcinoma and acute lymphocytic leukemia, it is likely that CCR9 plays a key in the survival and proliferation these cells. Thus, blocking the signaling of CCR9 should help prevent their expansion and metastasis.

Modulators of the Invention

[0048] The modulators of the present invention are of the following formula (I) or a salt thereof:



[0049] L is -C(O)-, -S-, -S(O)- or $-S(O)_2-$.

[0050] X represents from 1 to 4 substituents independently selected from the group consisting of halogen, -CN, -OH, $-OR^1$, $-C(O)R^1$, $-CO_2R^1$, $-O(CO)R^1$, $-C(O)NR^1R^2$, $-OC(O)NR^1R^2$, $-SR^1$, $-SOR^1$, $-SO_2R^1$, $-SO_2NR^1R^2$, $-NR^1R^2$, $-NR^1C(O)R^2$, $-NR^1C(O)_2R^2$, $-NR^1SO_2R^2$, $-NR^1(CO)NR^1R^2$, unsubstituted C_{2-8} alkyl, substituted C_{1-8} alkyl, unsubstituted or substituted C_{2-8} alkenyl, unsubstituted or substituted C_{2-8} alkynyl, unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted 6- to 10-membered aryl, unsubstituted or substituted 5- to 10-membered heteroaryl, and unsubstituted or substituted 3- to 10-membered heterocyclyl.

[0051] R^1, R^2 and R^3 are each independently selected from the group consisting of hydrogen, unsubstituted or substituted C_{1-6} haloalkyl, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{3-6} cycloalkyl, unsubstituted or substituted C_{2-6} alkenyl, unsubstituted or

substituted C_{2-6} alkynyl, unsubstituted or substituted 6- to 10-membered aryl, unsubstituted or substituted 5- to 10-membered heteroaryl, unsubstituted or substituted aryl-C_{1-4} alkyl, unsubstituted or substituted aryl-C_{1-4} alkyl, and unsubstituted or substituted aryloxy-C_{1-4} alkyl; or two of R^1, R^2 and R^3 together with the atom(s) to which they are attached, may form an unsubstituted or substituted 5-, 6- or 7- membered ring.

[0052] Y represents from 1 to 3 substituents, each independently selected from the group consisting of halogen, -CN, -OH, $-OR^4$, $-C(O)R^4$, $-CO_2R^4$, $-SR^4$, $-SOR^4$, $-SO_2R^4$, and unsubstituted or substituted C_{1-4} alkyl.

[0053] R^4 is selected from the group consisting of hydrogen, unsubstituted or substituted C_{1-6} haloalkyl, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{3-6} cycloalkyl, unsubstituted or substituted C_{2-6} alkenyl, and unsubstituted or substituted C_{2-6} alkynyl.

[0054] Z represents 0 to 5 substituents independently selected from the group consisting of halogen, unsubstituted or substituted C_{1-8} alkyl, unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{2-8} alkenyl, unsubstituted or substituted C_{2-8} alkynyl, unsubstituted or substituted C_{1-8} alkoxy, =O, -CN, $-NO_2$, -OH, $-OR^7$, $-OC(O)R^7$, $-CO_2R^7$, $-C(O)R^7$, $-CONR^7R^8$, $-OC(O)NR^7R^8$, $-NR^7C(O)R^8$, $-NR^7C(O)NR^8R^9$, $-NR^7R^8$, $-NR^7CO_2R^8$, $-SR^7$, $-SOR^7$, $-SO_2R^7$, $-SO_2NR^7R^8$, $-NR^7SO_2R^8$, unsubstituted or substituted 6- to 10-membered aryl, unsubstituted or substituted heteroaryl and unsubstituted or substituted heterocyclyl.

[0055] R^7, R^8 and R^9 are each independently hydrogen, unsubstituted or substituted C_{1-6} haloalkyl, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{3-6} cycloalkyl, unsubstituted or substituted C_{2-6} alkenyl, unsubstituted or substituted C_{2-6} alkynyl, unsubstituted or substituted phenyl, unsubstituted or substituted heteroaryl, unsubstituted or substituted aryl-C_{1-4} alkyl, and unsubstituted or substituted aryloxy-C_{1-4} alkyl; or where any two of R^7, R^8 and R^9 together with the atom(s) to which they are attached, may form a 5-, 6- or 7- membered ring.

Preferred L substituents

[0056] L is preferably –CO-.

Preferred X substituents

[0057] In one embodiment, at least one X substituent is preferably situated *para, meta,* or *ortho* to the sulfonamido bond as defined in formula (I).

[0058] In another embodiment, X preferably represents from 1 to 3 substituents independently selected from the group consisting of halogen, -CN, -OH, $-OR^1$, $-C(O)R^1$, $-CO_2R^1$, $-O(CO)R^1$, $-OC(O)NR^1R^2$, $-SR^1$, $-SOR^1$, $-SO_2R^1$, $-NR^1R^2$, $-NR^1C(O)R^2$, $-NR^1C(O)_2R^2$, $-NR^1(CO)NR^1R^2$, unsubstituted C_{2-8} alkyl, substituted C_{1-8} alkyl, unsubstituted or substituted C_{2-8} alkenyl, unsubstituted or substituted C_{2-8} alkynyl, unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted 6- to 10-membered aryl, unsubstituted or substituted 5- or 6-membered heteroaryl, or unsubstituted or substituted 3- to 7-membered heterocyclyl.

[0059] In another embodiment, at least one X is preferably unsubstituted C_{2-8} alkyl, unsubstituted C_{3-8} cycloalkyl, unsubstituted C_{2-8} alkenyl, or unsubstituted C_{2-8} alkynyl.

[0060] In another embodiment, at least one X is substituted C_{1-8} alkyl, substituted C_{3-8} cycloalkyl, substituted C_{2-8} alkenyl, or substituted C_{2-8} alkynyl, each having from 1 to 5 substituents independently selected from the group consisting of halogen, -OH, -CN, $-NO_2$, =O, $-OC(O)R^1$, $-OR^1$, $-C(O)R^1$, $-CONR^1R^2$, $-OC(O)NR^1R^2$, $-NR^2C(O)R^1$, $-NR^1C(O)NR^2R^3$, $-CO_2R^1$, $-NR^1R^2$, $-NR^2CO_2R^1$, $-SR^1$, $-SOR^1$, $-SO_2R^1$, $-SO_2NR^1R^2$, $-NR^1SO_2R^2$, unsubstituted or substituted 6- to 10-membered aryl, unsubstituted or substituted 5- to 10-membered heteroaryl, and unsubstituted or substituted 3- to 10- membered heterocyclyl.

[0061] In another embodiment, at least one X is substituted C_{1-8} alkyl, having from 1 to 3 substituents independently selected from the group consisting of halogen, -OH, -CN, =O, $-OC(O)R^1$, $-OR^1$, $-C(O)R^1$, $-CONR^1R^2$, -

$NR^2C(O)R^1$, $-CO_2R^1$, $-NR^1R^2$, $-SO_2R^1$, unsubstituted or substituted phenyl, and unsubstituted or substituted 5- or 6-membered heteroaryl.

[0062] In another embodiment, at least one X is unsubstituted or substituted 6- to 10-membered aryl, unsubstituted or substituted 5- to 10-membered heteroaryl, or unsubstituted or substituted 3- to 10-membered heterocyclyl, where when X is substituted is has from 1 to 4 substituents independently selected from the group consisting of halogen, unsubstituted or substituted C_{1-8} alkyl, -CN, $-NO_2$, -OH, $-OR^1$, =O, $-OC(O)R^1$, $-CO_2R^1$, $-C(O)R^1$, $-CONR^1R^2$, $-OC(O)NR^1R^2$, $-NR^2C(O)R^1$, $-NR^1C(O)NR^2R^3$, $-NR^1R^2$, $-NR^2CO_2R^1$, $-SR^1$, $-SOR^1$, $-SO_2R^1$, $-SO_2NR^1R^2$, and $-NR^1SO_2R^2$.

[0063] In another embodiment, at least one X is unsubstituted or substituted phenyl, where when X is substituted it has from 1 to 3 substituents independently selected from the group consisting of halogen, -OH, $-OR^1$, $-C(O)R^1$, $-CONR^1R^2$, $-NR^2C(O)R^1$, $-NR^1R^2$, $-SO_2R^1$, and unsubstituted or substituted C_{1-8} alkyl.

[0064] In another embodiment, at least one X is unsubstituted or substituted 5- or 6-membered heteroaryl, where when X is substituted it has from 1 to 3 substituents independently selected from the group consisting of halogen, -OH, $-OR^1$, $-C(O)R^1$, $-CONR^1R^2$, $-NR^2C(O)R^1$, $-NR^1R^2$, $-SO_2R^1$, and unsubstituted or substituted C_{1-8} alkyl.

[0065] In another embodiment, at least one X is unsubstituted or substituted 3- to 7-membered heterocyclyl, where when X is substituted it has from 1 to 3 substituents independently selected from the group consisting of C_{1-8} alkyl, $-OR^1$, -OH, $-OC(O)R^1$, $-CO_2R^1$, $-C(O)R^1$, $-CONR^1R^2$, $-NR^1R^2$, $-SO_2R^1$, and $-NR^1SO_2R^2$.

[0066] R^1, R^2 and R^3, when substituted, preferably can have from 1 to 3 substituents independently selected from the group consisting of halogen, -OH, -OR', -OCOHNR', $-OCONR'_2$, -SH, -SR', $-SO_2NH_2$, $-CONH_2$, $-NHC(O)NH_2$, $NR'C(O)NH_2$, $-CO_2H$, -CN, $-NO_2$, $-NH_2$, -NHR' and $-NR'_2$, $-S(O)R'$, $-S(O)_2R'$, $-CO_2R'$, $-CONR'_2$, -CONHR', -C(O)R', -NR'COR', -NHCOR', $-NR'CO_2R'$, $-NHCO_2R'$, $-CO_2R'$, $-NR'C(O)NR'_2$, $-NHC(O)NR'_2$, -

NR'C(O)NHR', -NHC(O)NHR', -NR'SO_2R', -NHSO_2R', -SO_2NR'$_2$, and -SO_2NHR', where R' is C_{1-6}alkyl.

Preferred Y substituents

[0067] In one embodiment, Y represents from 1 to 3 substituents independently selected from the group consisting of halogen, -CN, -OR^4, -C(O)R^4, -SR^4, -CF_3, -SOR^4, and -SO_2R^4.

[0068] In another embodiment, Y preferably represents from 1 to 3 substituents independently selected from the group consisting of halogen, -CN, -CF_3, and -SO_2R^4.

[0069] In another embodiment, at least one Y preferably represents halogen.

[0070] In another embodiment, Y preferably represents from 1 to 2 substituents, each independently selected from the group consisting of halogen, -CN, -OH, -OR^4, -C(O)R^4, -CO_2R^4, -SR^4, -SOR^4, -SO_2R^4, and unsubstituted or substituted C_{1-4} alkyl.

[0071] In another embodiment, one Y preferably represents a halogen and another substituent selected from the group consisting of halogen, -CN, -OH, -OR^4, -C(O)R^4, -CO_2R^4, -SR^4, -SOR^4, -SO_2R^4 and unsubstituted or substituted C_{1-4} alkyl.

[0072] In another embodiment, at least one Y substituent preferably is located *para* to the sulfonamide bond as defined in formula (I) and another Y substituent is halogen.

[0073] In another embodiment, at least one Y is preferably unsubstituted C_{1-4} alkyl.

[0074] In another embodiment, at least one Y is preferably substituted C_{1-4} alkyl, having from 1 to 3 substituents independently selected from the group consisting of halogen, -OH, -OR^4, -CN, -NO_2, =O, -OC(O)R^4, -CO_2R^4, -C(O)R^4, -CONR^{4}R^5, -OC(O)NR^{4}R^5, -NR^{4}C(O)R^5, -NR^{4}C(O)NR^{5}R^6, -NR^{4}R^5, -NR^4CO_2R^5, -SR^4, -SOR^4, -SO_2R^4, -SO_2NR^{4}R^5, and -NR^4SO_2R^5.

[0075] where R^4, R^5 and R^6 are each independently selected from the group consisting of hydrogen, halogen, unsubstituted or substituted

C_{1-6} alkyl, unsubstituted or substituted C_{3-6} cycloalkyl, unsubstituted or substituted C_{2-6} alkenyl, and unsubstituted or substituted C_{2-6} alkynyl; or where any two of R^4, R^5 and R^6 together with the atom(s) to which they are attached, may form a 5-, 6- or 7-membered ring.

[0076] In another embodiment, Y is preferably substituted C_{1-4} alkyl, having from 1 to 3 substituents independently selected from the group consisting of halogen, -OH, $-OR^4$, -CN, $-NO_2$, =O, $-OC(O)R^4$, $-CO_2R^4$, $-C(O)R^4$, $-CONR^4R^5$, $-NR^4C(O)R^5$, $-NR^4R^5$, $-NR^4$, $-SR^4$, $-SOR^4$, $-SO_2R^4$, and $-NR^4SO_2R^5$.

[0077] R^4, R^5 and R^6, when substituted, preferably can have from with from 1 to 3 substituents independently selected from the group consisting of -OH, -OR', -SH, -SR', $-SO_2NH_2$, $-CONH_2$, $-NHC(O)NH_2$, $N(C_{1-6}alkyl)C(O)NH_2$, $-CO_2H$, -CN, $-NO_2$, $-NH_2$, -NHR', $-NR'_2$, -S(O)R', $-S(O)_2R'$, $-CO_2R'$, -CONHR', $-CONR'_2$, and -C(O)R', where R' is C_{1-6}alkyl.

Preferred Z substituents

[0078] In one embodiment, Z preferably represents 0 to 3 substituents independently selected from the group consisting of halogen, unsubstituted or substituted C_{1-8} alkyl, unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{2-8} alkenyl, unsubstituted or substituted C_{2-8} alkynyl, unsubstituted or substituted C_{1-8} alkoxy, =O, -CN, $-NO_2$, -OH, $-OR^7$, $-OC(O)R^7$, $-CO_2R^7$, $-C(O)R^7$, $-CONR^7R^8$, $-NR^7C(O)R^8$, $-NR^7R^8$, $-SR^7$, $-SOR^7$, $-SO_2R^7$, $-SO_2NR^7R^8$, $-NR^7SO_2R^8$, unsubstituted or substituted phenyl, unsubstituted or substituted 5- or 6-membered heteroaryl, and unsubstituted or substituted 3- to 7-membered heterocyclyl.

[0079] In another embodiment, Z preferably represents 0 to 2 substituents independently selected from the group consisting of halogen, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{1-6} alkoxy, =O, -CN, $-NO_2$, -OH, $-OR^7$, $-C(O)R^7$, $-CONR^7R^8$, $-NR^7C(O)R^8$, $-NR^7R^8$, $-SR^7$, $-SOR^7$, $-SO_2R^7$, $-SO_2NR^7R^8$, $-NR^7SO_2R^8$, unsubstituted or substituted phenyl, unsubstituted or substituted 3 to 7-membered heterocycyl, and unsubstituted or substituted 5- or 6-membered heteroaryl.

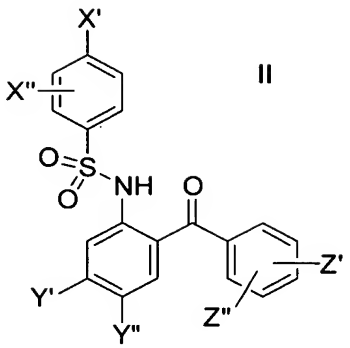
[0080] In another embodiment, at least one Z preferably is unsubstituted C_{1-8} alkyl, unsubstituted C_{3-8} cycloalkyl, unsubstituted C_{2-8} alkenyl, unsubstituted C_{2-8} alkynyl or unsubstituted C_{1-8} alkoxy, unsubstituted 6- to 10- membered aryl, unsubstituted 3- to 7-membered heterocyclyl, and 3- to 7-membered heteraryl.

[0081] In another embodiment, at least one Z is preferably substituted C_{1-8} alkyl, substituted C_{3-8} cycloalkyl, substituted C_{2-8} alkenyl, substituted C_{2-8} alkynyl or substituted C_{1-8} alkoxy, each having from 1 to 5 substituents independently selected from the group consisting of halogen, -OH, -OR^7, -CN, -NO_2, =O, -CN, -NO_2, -$OC(O)R^7$, -CO_2R^7, -$C(O)R^7$, -$CONR^7R^8$, -$OC(O)NR^7R^8$, -$NR^7C(O)R^8$, -$NR^7C(O)NR^8R^9$, -NR^7R^8, -$NR^7CO_2R^8$, -SR^7, -SOR^7, -SO_2R^7, -$SO_2NR^7R^8$, -$NR^7SO_2R^8$, unsubstituted or substituted phenyl, unsubstituted or substituted 5- or 6- membered heteroaryl, or unsubstituted or substituted 3- to 6-membered heterocyclyl.

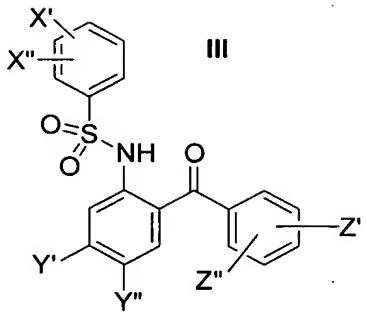
[0082] R^7, R^8 and R^9, when substituted, preferably can have from 1 to 3 substituents independently selected from the group consisting of halogen, -OH, -OR', -OCONHR', -$OCONR'_2$, -SH, -SR', -CN, -SO_2NH_2, -$CONH_2$, -$NHC(O)NH_2$, -$NR'C(O)NH_2$, -CO_2H, -NO_2, -NH_2, -NHR' and -NR'_2, -$S(O)R'$, -$S(O)_2R'$, -CO_2R', -$CONR'_2$, -CONHR', -C(O)R', -NR'COR', -NHCOR', -$NR'CO_2R'$, -$NHCO_2R'$, -CO_2R', -$NR'C(O)NR'_2$, -$NHC(O)NR'_2$, -$NR'C(O)NHR'$, -NHC(O)NHR', -$NR'SO_2R'$, -$NHSO_2R'$, -$SO_2NR'_2$, and -SO_2NHR', where R' is C_{1-6}alkyl.

Preferred modulators

[0083] The modulators of the present invention are preferably of the formulae:



II



III

[0084] X' and X" are each independently selected from the group consisting of hydrogen, halogen, -CN, -OH, $-OR^1$, $-C(O)R^1$, $-CO_2R^1$, $-O(CO)R^1$, $-C(O)NR^1R^2$, $-OC(O)NR^1R^2$, $-SR^1$, $-SOR^1$, $-SO_2R^1$, $-SO_2NR^1R^2$, $-NR^1R^2$, $-NR^1C(O)R^2$, $-NR^1C(O)_2R^2$, $-NR^1SO_2R^2$, $-NR^1(CO)NR^2R^3$, unsubstituted or substituted C_{1-8} alkyl, unsubstituted or substituted C_{2-8} alkenyl, unsubstituted or substituted C_{2-8} alkynyl, unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted 6- to 10-membered aryl, unsubstituted or substituted 5- to 10-membered heteroaryl, and unsubstituted or substituted 3- to 10-membered heterocyclyl, with the proviso that if one of X' and X" is hydrogen than the other is not hydrogen or unsubstituted methyl.

[0085] R^1, R^2 and R^3 are each independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, 6- to 10-membered aryl, 5- to 10-membered heteroaryl, aryl-C_{1-4} alkyl, aryl-C_{1-4} alkyl, and aryloxy-C_{1-4} alkyl; or two of R^1, R^2 and R^3 together with the atom(s) to which they are attached, may form a 5-, 6- or 7- membered ring.

[0086] Y' and Y" are each independently selected from the group consisting of hydrogen, halogen, -CN, -OH, $-OR^4$, $-C(O)R^4$, $-CO_2R^4$, $-SR^4$, $-SOR^4$, $-SO_2R^4$, and unsubstituted or substituted C_{1-4} alkyl, with the proviso that Y' and Y" cannot both be hydrogen simultaneously.

[0087] R^4 is selected from the group consisting of hydrogen, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{3-6} cycloalkyl, unsubstituted or substituted C_{2-6} alkenyl, and unsubstituted or substituted C_{2-6} alkynyl.

[0088] Z' and Z" are each independently selected from the group consisting of hydrogen, halogen, unsubstituted or substituted C_{1-8} alkyl,

unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{2-8} alkenyl, unsubstituted or substituted C_{2-8} alkynyl, unsubstituted or substituted C_{1-8} alkoxy, =O, -CN, $-NO_2$, -OH, $-OR^7$, $-OC(O)R^7$, $-CO_2R^7$, $-C(O)R^7$, $-CONR^7R^8$, $-OC(O)NR^7R^8$, $-NR^7C(O)R^8$, $-NR^7C(O)NR^8R^9$, $-NR^7R^8$, $-NR^7CO_2R^8$, $-SR^7$, $-SOR^7$, $-SO_2R^7$, $-SO_2NR^7R^8$, $-NR^7SO_2R^8$, unsubstituted or substituted 6- to 10-membered aryl, unsubstituted or substituted 5- or 6-membered heteroaryl and unsubstituted or substituted 3- to 7-membered heterocyclyl.

[0089] R^7, R^8 and R^9 are each independently hydrogen, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted C_{3-6} cycloalkyl, unsubstituted or substituted C_{2-6} alkenyl, unsubstituted or substituted C_{2-6} alkynyl, unsubstituted or substituted phenyl, unsubstituted or substituted heteroaryl, unsubstituted or substituted aryl-C_{1-4} alkyl, and unsubstituted or substituted aryloxy-C_{1-4} alkyl; or where any two of R^7, R^8 and R^9 together with the atom(s) to which they are attached, may form a 5-, 6- or 7- membered ring.

[0090] In one embodiment, X' and X" are each independently selected from the group consisting of hydrogen, halogen, -CN, $-OR^1$, $-C(O)R^1$, $-SO_2R^1$, $-NR^1R^2$, unsubstituted or substituted C_{1-8} alkyl, unsubstituted or substituted C_{3-8} cycloalkyl, unsubstituted or substituted C_{2-8} alkenyl, unsubstituted or substituted phenyl, unsubstituted or substituted 5- or 6-membered heteroaryl, unsubstituted or substituted 5- or 6-membered heterocyclyl, with the proviso that if one of X' and X" is hydrogen than the other is not hydrogen or unsubstituted methyl.

[0091] In another embodiment, X' and X" are each independently selected from the group consisting of hydrogen, halogen, -CN, $-CF_3$, $-CH=CH_2$, isoamyl, phenylacetylene, t-butyl, ethyl (Et), i-propyl (^{i}Pr), $-C(CH_3)_2CH_2CH_3$, hydroxybutyl, $-C(CH_3)_2CH_2CH_2OH$, $-CH_2CH_2CO_2Me$, $-OCF_3$, -OMe, -O-^{i}Pr, -C(O)Me, $-SO_2Me$, phenyl (Ph), -OEt, pyrazole, thiophene, aminopyridine, oxazole, and morpholinyl, with the proviso that X' and X" cannot both be hydrogen simultaneously.

[0092] In one embodiment, Y' and Y" are each independently hydrogen or halogen, with the proviso that one or both are halogen.

[0093] In another embodiment, Y' is hydrogen and Y" is chloro or bromo.

[0094] In another embodiment, at least one of Y' or Y" is a halogen atom and is *ortho* or *meta* or *para* to the sulfonamide bond in formula (I).

[0095] In one embodiment, Z' and Z" are each independently selected from the group consisting of hydrogen, halogen, unsubstituted or substituted C_{1-8} alkyl, unsubstituted or substituted C_{3-8} cycloalkyl, -CN, -OH, $-OR^7$, $-C(O)R^7$, $-CO_2R^7$, $-OC(O)R^7$, $-CONR^7R^8$, $-NR^7R^8$, $-NR^7CO_2R^8$, $-SR^7$, $-SOR^7$, $-SO_2R^7$, $-NR^7SO_2R^8$, $-SO_2NR^7R^8$, unsubstituted or substituted phenyl, and unsubstituted or substituted 5- or 6-membered heteroaryl, unsubstituted or substituted 3- to 7-membered heterocycyl.

[0096] In another embodiment, Z' and Z" are each independently hydrogen, halogen, -CN, $-OR^7$, $-NR^7R^8$, $-SR^7$, $-SOR^7$, and $-SO_2R^7$, unsubstituted or substituted C_{1-6} alkoxyl, unsubstituted or substituted C_{1-6} alkyl, unsubstituted or substituted phenyl, or unsubstituted or substituted 5- or 6-membered heterocyclyl.

Known compounds

[0097] The following compound are known, but not as chemokine modulators, and more specifically not as CCR9 modulators (these compounds are explicitly excluded from modulators of formula (I)):

- N-(2-benzoyl-4-methylphenyl)-4-chloro-benzenesulfonamide;
- N-(2-benzoylphenyl)-3,5-bis(trifluoromethyl)-benzenesulfonamide;
- N-(4-amino-2-benzoylphenyl)-4-methoxy-benzenesulfonamide;
- N-[4-[[(2-benzoyl-4-chlorophenyl)amino]sulfonyl]phenyl]-acetamide;
- N-(2-benzoyl-4-chlorophenyl)-4-ethyl-benzenesulfonamide;
- N-(2-benzoylphenyl)-4-chloro-benzenesulfonamide;
- N-(2-benzoyl-4-chlorophenyl)-2,5-dichloro-benzenesulfonamide;
  N-(2-benzoyl-4-chlorophenyl)-2,4,6-trimethyl-benzenesulfonamide;
  N-(2-benzoyl-4-chlorophenyl)-2,4,6-tris(1-methylethyl)-benzenesulfonamide;

- N-(2-benzoyl-4-chlorophenyl)-4-methoxy-benzenesulfonamide;
- N-(2-benzoyl-4-chlorophenyl)-4-tricyclo[3.3.1.13,7]dec-1-yl-benzenesulfonamide;
- N-(2-benzoyl-4-chlorophenyl)-2,4-dichloro-benzenesulfonamide;
- N-(2-benzoyl-4-chlorophenyl)-4-bromo-benzenesulfonamide;
- N-(2-benzoyl-4-chlorophenyl)-4-chloro-benzenesulfonamide;
- N-(2-benzoyl-4-chlorophenyl)-4-fluoro-benzenesulfonamide;
- N-[4-bromo-2-(2-fluorobenzoyl)phenyl]-3,4-dimethoxy-benzenesulfonamide;
- N-[4-chloro-2-(2-chlorobenzoyl)phenyl]-4-(2-propenyloxy)-benzenesulfonamide;
- N-[4-chloro-2-(2-chlorobenzoyl)phenyl]-3,4-dimethoxy-benzenesulfonamide;
- N-[4-chloro-2-(2-chlorobenzoyl)phenyl]-2,5-dimethoxy-benzenesulfonamide;
- 2-amino-N-(2-benzoyl-4-methylphenyl)-benzenesulfonamide;
- N-(2-benzoyl-5-methylphenyl)-N,4-dimethyl-benzenesulfonamide;
- 2-amino-2'-benzoyl-4'-chloro-benzenesulfonanilide.

[0098] Modulators of the present invention preferably exclude compounds where:

- L is carbonyl, at least one X is 2- or 4-methoxy, Y is 4-halo, and Z is 2-halo or hydrogen.
- L is carbonyl, at least one X is 4-methoxy, Y is 4-amino, and Z is hydrogen.
- L is carbonyl; X is 2,4,6-trialkyl, 4-ethyl, or 4-acetamido; Y is 4-chloro; and Z is hydrogen.
- L is carbonyl, X is 2-amino, Y is 4-amino or 4-chloro; and Z is hydrogen.

  L is carbonyl; X is 4-halo; Y is hydrogen, 4-chloro or 4-methyl; and Z is hydrogen.

L is carbonyl; X is 2-choro; Y is 4-chloro; and Z is 2-choro.

Compositions that Modulate CCR9 Activity

[0099] In another aspect, the present invention provides compositions that modulate CCR9 activity. Generally, the compositions for modulating chemokine receptor activity in humans and animals will comprise a pharmaceutically acceptable excipient or diluent and a compound having the formula provided above as formula (I).

[00100] The term "composition" as used herein is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

[00101] The pharmaceutical compositions for the administration of the compounds of this invention may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general, the pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition the active object compound is included in an amount sufficient to produce the desired effect upon the process or condition of diseases.

[00102] The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions and self emulsifications as described in U.S. Patent Application 20020012680, hard or soft capsules, or syrups or elixirs.

Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions. Such compositions may contain one or more agents selected from sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with other non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents such as cellulose, silicon dioxide, aluminum oxide, calcium carbonate, sodium carbonate, glucose, mannitol, sorbitol, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example PVP, cellulose, PEG, starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc,. The tablets may be uncoated or they may be coated enterically or otherwise by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in the U.S. Pat. Nos. 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

[00103] Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil. Additionally, emulsions can be prepared with a non-water miscible ingredient such as oils and stabilized with surfactants such as mono-diglycerides, PEG esters and the like.

[00104] Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose,

sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

[00105] Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti oxidant such as ascorbic acid.

[00106] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

[00107] The pharmaceutical compositions of the invention may also be in the form of oil in water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be

naturally-occurring gums, for example gum acacia or gum tragacanth, naturally occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan rnonooleate. The emulsions may also contain sweetening and flavoring agents.

[00108] Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative. and flavoring and coloring agents. Oral solutions can be prepared in combination with, for example, cyclodextrin, PEG and surfactants.

[00109] The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, axed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

[00110] The compounds of the present invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols. Additionally, the compounds can be administered via ocular delivery by means of solutions or

ointments. Still further, transdermal delivery of the subject compounds can be accomplished by means of iontophoretic patches and the like.

[00111] For topical use, creams, ointments, jellies, solutions or suspensions containing the compounds of the present invention are employed. As used herein, topical application is also meant to include the use of mouth washes and gargles.

[00112] The pharmaceutical compositions and methods of the present invention may further comprise other therapeutically active compounds as noted herein, such as those applied in the treatment of the above mentioned pathological conditions.

Methods of Treating CCR9-mediated Conditions or Diseases

[00113] In yet another aspect, the present invention provides methods of treating or preventing a CCR9-mediated condition or disease by administering to a subject having such a condition or disease a therapeutically effective amount of any compound of formula (I) above. Compounds for use in the present methods include those compounds according to formula (I), those provided above as embodiments, those specifically exemplified in the Examples below, and those provided with specific structures herein. The "subject" is defined herein to include animals such as mammals, including, but not limited to, primates (e.g., humans), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice and the like. In preferred embodiments, the subject is a human.

[00114] As used herein, the phrase "CCR9-mediated condition or disease" and related phrases and terms refer to a condition or disease characterized by inappropriate, i.e., less than or greater than normal, CCR9 functional activity. Inappropriate CCR9 functional activity might arise as the result of CCR9 expression in cells which normally do not express CCR9, increased CCR9 expression (leading to, e.g., inflammatory and immunoregulatory disorders and diseases) or decreased CCR9 expression. Inappropriate CCR9 functional activity might also arise as the result of TECK secretion by cells which normally do not secrete TECK, increased TECK

expression (leading to, *e.g.*, inflammatory and immunoregulatory disorders and diseases) or decreased TECK expression. A CCR9-mediated condition or disease may be completely or partially mediated by inappropriate CCR9 functional activity. However, a CCR9-mediated condition or disease is one in which modulation of CCR9 results in some effect on the underlying condition or disease (*e.g.*, a CCR9 antagonist results in some improvement in patient well being in at least some patients).

[00115] The term "therapeutically effective amount" means the amount of the subject compound that will elicit the biological or medical response of a cell, tissue, system, or animal, such as a human, that is being sought by the researcher, veterinarian, medical doctor or other treatment provider.

[00116] Diseases and conditions associated with inflammation, immune disorders, infection and cancer can be treated or prevented with the present compounds, compositions, and methods. In one group of embodiments, diseases or conditions, including chronic diseases, of humans or other species can be treated with inhibitors of CCR9 function. These diseases or conditions include: (1) allergic diseases such as systemic anaphylaxis or hypersensitivity responses, drug allergies, insect sting allergies and food allergies, (2) inflammatory bowel diseases, such as Crohn's disease, ulcerative colitis, ileitis and enteritis, (3) vaginitis, (4) psoriasis and inflammatory dermatoses such as dermatitis, eczema, atopic dermatitis, allergic contact dermatitis, urticaria and pruritus, (5) vasculitis, (6) spondyloarthropathies, (7) scleroderma, (8) asthma and respiratory allergic diseases such as allergic asthma, allergic rhinitis, hypersensitivity lung diseases and the like, (9) autoimmune diseases, such as fibromyalagia, scleroderma, ankylosing spondylitis, juvenile RA, Still's disease, polyarticular juvenile RA, pauciarticular juvenile RA, polymyalgia rheumatica, rheumatoid arthritis, psoriatic arthritis, osteoarthritis, polyarticular arthritis, multiple sclerosis, systemic lupus erythematosus, type I diabetes, type II diabetes, glomerulonephritis, and the like, (10) graft rejection (including allograft rejection), (11) graft-v-host disease (including both acute and chronic),

(12) other diseases in which undesired inflammatory responses are to be inhibited, such as atherosclerosis, myositis, neurodegenerative diseases (*e.g.*, Alzheimer's disease), encephalitis, meningitis, hepatitis, nephritis, sepsis, sarcoidosis, allergic conjunctivitis, otitis, chronic obstructive pulmonary disease, sinusitis, Behcet's syndrome and gout, (13) immune mediated food allergies such as Coeliac (Celiac) disease (14) pulmonary fibrosis and other fibrotic diseases, and (15) irritable bowel syndrome.

[00117] In another group of embodiments, diseases or conditions can be treated with modulators and agonists of CCR9 function. Examples of diseases to be treated by modulating CCR9 function include cancers, cardiovascular diseases, diseases in which angiogenesis or neovascularization play a role (neoplastic diseases, retinopathy and macular degeneration), infectious diseases (viral infections, *e.g.*, HIV infection, and bacterial infections) and immunosuppressive diseases such as organ transplant conditions and skin transplant conditions. The term "organ transplant conditions" is means to include bone marrow transplant conditions and solid organ (*e.g.*, kidney, liver, lung, heart, pancreas or combination thereof) transplant conditions.

[00118] Preferably, the present methods are directed to the treatment of diseases or conditions selected from inflammatory bowel disease including Crohn's disease and Ulcerative Colitis, allergic diseases, psoriasis, atopic dermatitis and asthma, autoimmune disease such as rheumatoid arthritis and immune-mediated food allergies such as Coelaic disease.

[00119] Depending on the disease to be treated and the subject's condition, the compounds and compositions of the present invention may be administered by oral, parenteral (*e.g.*, intramuscular, intraperitoneal, intravenous, ICV, intracisternal injection or infusion, subcutaneous injection, or implant), inhalation, nasal, vaginal, rectal, sublingual, or topical routes of administration and may be formulated, alone or together, in suitable dosage unit formulations containing conventional non toxic pharmaceutically acceptable carriers, adjuvants and vehicles appropriate for each rouse of

administration. The present invention also contemplates administration of the compounds and compositions of the present invention in a depot formulation.

[00120] In the treatment or prevention of conditions which require chemokine receptor modulation an appropriate dosage level will generally be about 0.001 to 100 mg per kg patient body weight per day which can be administered in single or multiple doses. Preferably, the dosage level will be about 0.01 to about 25 mg/kg per day; more preferably about 0.05 to about 10 mg/kg per day. A suitable dosage level may be about 0.01 to 25 mg/kg per day, about 0.05 to 10 mg/kg per day, or about 0.1 to 5 mg/kg per day. Within this range the dosage may be 0.005 to 0.05, 0.05 to 0.5, 0.5 to 5.0, or 5.0 to 50 mg/kg per day. For oral administration, the compositions are preferably provided in the form of tablets containing 1.0 to 1000 milligrams of the active ingredient, particularly 1.0, 5.0, 10.0, 15.0, 20.0, 25.0, 50.0, 75.0, 100.0, 150.0, 200.0, 250.0, 300.0, 400.0, 500.0, 600.0, 750.0, 800.0, 900.0, and 1000.0 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

[00121] It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, hereditary characteristics, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

[00122] In still other embodiments, the present methods are directed to the treatment of allergic diseases, wherein a compound or composition of the invention is administered either alone or in combination with a second therapeutic agent, wherein said second therapeutic agent is an antihistamine. When used in combination, the practitioner can administer a combination of the compound or composition of the present invention and a

second therapeutic agent. Also, the compound or composition and the second therapeutic agent can be administered sequentially, in any order.

[00123] In yet other embodiments, the present methods are directed to the treatment of psoriasis wherein a compound or composition of the invention is used alone or in combination with a second therapeutic agent selected from a corticosteroid, a lubricant, a keratolytic agent, a vitamin D_3 derivative, PUVA and anthralin.

[00124] In other embodiments, the present methods are directed to the treatment of atopic dermatitis using a compound or composition of the invention either alone or in combination with a second therapeutic agent selected from a lubricant and a corticosteroid.

[00125] In further embodiments, the present methods are directed to the treatment of asthma using a compound or composition of the invention either alone or in combination with a second therapeutic agent selected from a β2-agonist and a corticosteroid.

[00126] The compounds and compositions of the present invention can be combined with other compounds and compositions having related utilities to prevent and treat the condition or disease of interest, such as inflammatory conditions and diseases, including inflammatory bowel disease, allergic diseases, psoriasis, atopic dermatitis and asthma, and those pathologies noted above.

[00127] The weight ratio of the compound of the present invention to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the present invention is combined with an NSAID the weight ratio of the compound of the present invention to the NSAID will generally range from about 1000:1 to about 1:1000, preferably about 200:1 to about 1:200. Combinations of a compound of the present invention and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

[00128]

EXAMPLES

[00129] Reagents and solvents used below can be obtained from commercial sources such as Aldrich Chemical Co. (Milwaukee, Wisconsin, USA). ^{1}H-NMR were recorded on a Varian Mercury 400 MHz NMR spectrometer. Significant peaks are tabulated in the order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet) and number of protons. Mass spectrometry results are reported as the ratio of mass over charge, followed by the relative abundance of each ion (in parenthesis). In tables, a single m/e value is reported for the M+H (or, as noted, M-H) ion containing the most common atomic isotopes. Isotope patterns correspond to the expected formula in all cases. Electrospray ionization (ESI) mass spectrometry analysis was conducted on a Hewlett-Packard MSD electrospray mass spectrometer using the HP1100 HPLC for sample delivery. Normally the analyte was dissolved in methanol at 0.1 mg/mL and 1 μL was infused with the delivery solvent into the mass spectrometer, which scanned from 100 to 1500 daltons. All compounds could be analyzed in the positive ESI mode, using acetonitrile / water with 1% formic acid as the delivery solvent. The compounds provided below could also be analyzed in the negative ESI mode, using 2mM NH_4OAc in acetonitrile / water as delivery system.

[00130] Compounds within the scope of this invention can be synthesized as described below, using a variety of reactions known to the skilled artisan. A sample of useful routes to both the benzophenone and heteroaryl derived subunits and to fully elaborated sulfonamide molecules of formula (I) within this claim are provided below. In the descriptions of the syntheses that follow, some precursors were obtained from commercial sources. These commercial sources include Aldrich Chemical Co., Acros Organics, Ryan Scientific Incorporated, Oakwood Products Incorporated, Lancaster Chemicals, Sigma Chemical Co., Lancaster Chemical Co., TCI-America, Alfa Aesar, Davos Chemicals, and GFS Chemicals.

[00131] Compounds of the invention can be prepared using conventional synthetic methodology. Examples of approaches that may be taken to synthesize these compounds are shown below. Nonetheless, one

skilled in the art will recognize that alternative methods may be employed to synthesize the target compounds of this invention, and that the approaches described within the body of this document are not exhaustive, but do provide broadly applicable and practical routes to compounds of interest.

[00132] Certain molecules claimed in this patent can exist in different enantiomeric and diastereomeric forms and all such variants of these compounds are within the scope of the invention.

[00133] The detailed description of the experimental procedures used to synthesize key compounds in this text lead to molecules that are described by the physical data identifying them as well as by the structural depictions associated with them.

[00134] Those skilled in the art will also recognize that during standard work up procedures in organic chemistry, acids and bases are frequently used. Salts of the parent compounds are sometimes produced, if they possess the necessary intrinsic acidity or basicity, during the experimental procedures described within this patent.

Preparation of CCR 9 modulators

[00135] The following examples are offered to illustrate, but not to limit, the claimed invention.

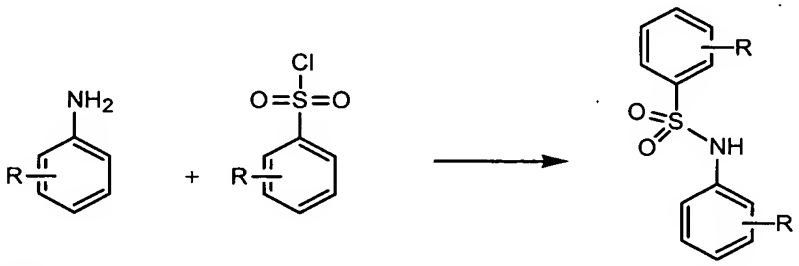
[00136] Additionally, those skilled in the art will recognize that the molecules claimed in this patent may be synthesized using a variety of standard organic chemistry transformations.

[00137] Certain general reaction types employed widely to synthesize target compounds in this invention are summarized in the examples. Specifically, generic procedures for sulfonamide formation, pyridine N-oxide formation and 2-aminophenyl-arylmethanone synthesis via Friedel-Crafts type approaches are given, but numerous other standard chemistries are described within and were employed routinely.

[00138] While not intended to be exhaustive, representative synthetic organic transformations which can be used to prepare compounds of the invention are included below.

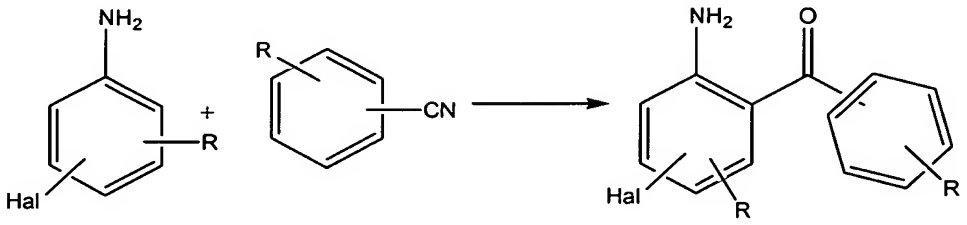
[00139] These representative transformations include; standard functional group manipulations; reduction such as nitro to amino; oxidations of functional groups including alcohols and pyridines; aryl substitutions via *IPSO* or other mechanisms for the introduction of a variety of groups including nitrile, methyl and halogen; protecting group introductions and removals; Grignard formation and reaction with an electrophile; metal-mediated cross couplings including but not limited to Buckvald, Suzuki and Sonigashira reactions; halogenations and other electrophilic aromatic substitution reactions; diazonium salt formations and reactions of these species; etherifications; cyclative condensations, dehydrations, oxidations and reductions leading to heteroaryl groups; aryl metallations and transmetallations and reaction of the ensuing aryl-metal species with an electrophile such as an acid chloride or Weinreb amide; amidations; esterifications; nucleophilic substitution reactions; alkylations; acylations; sulfonamide formation; chlorosulfonylations; ester and related hydrolyses, and the like.

Example 1: General Procedure for the preparation of N-Aryl-benzenesulfonamides.



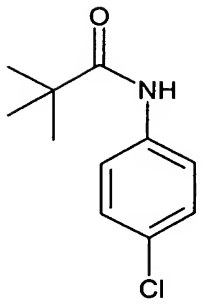
[00140] In the above general scheme, R represents 1 to 5 substituents consistent with the definitions provided above. To the desired aniline (0.5 mmol) dissolved in pyridine and cooled in an ice-water bath was added a solution of an aryl sulfonyl chloride (0.5 mmol) dissolved in cold pyridine. The reaction mixture was then heated to 60°C with gentle shaking for 16h. Evaporation of the solvent with standard workup followed by either flash chromatography or reversed phase HPLC yielded the corresponding N-aryl-benzenesulfonamides.

Example 2: General Procedure for the Synthesis of (2-Amino-phenyl)-aryl-methanon s



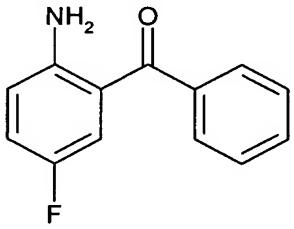
[00141] In the above general scheme, R represents 1 to 5 substituents consistent with the definitions provided above. To 12.5 mL 1 M BCl_3 (12 mmol, 1.2 eq.) in methylene chloride stirred at 0°C was added a solution of the desired haloaniline (10 mmol, 1.0 eq.) in 15 mL of TCE drop wise over 20 minutes. After 10 minutes the desired benzonitrile (11 mmol, 1.1 eq.) was added followed by $AlCl_3$ (15 mmol, 1.5 eq.). The reaction was brought to RT, stirred for an hour then heated at 80-90°C until all of the DCM was distilled off. The reaction mixture was then refluxed at 160°C for 4 hours, cooled to RT and stirred overnight. 10 mL 3 M HCl were carefully added and the mixture was refluxed at 120°C for 2-3 hours while reaction progress was monitored by LC/MS. The crude reaction was cooled to RT and 100 mL water was added. The crude mixture was extracted with DCM (2 x 50 mL), the aqueous layer was set aside and the organic layer was back extracted with 50 mL 1 M HCl (aq.). All aqueous layers were combined, brought to pH 12 with 3 M NaOH (aq.) and extracted with DCM (4 x 50 mL). The DCM layer was dried on Na_2SO_4, filtered and concentrated by rotary evaporation. The crude product was washed liberally with Et_2O and dried under vacuum, and further purified by conventional techniques such as column chromatography when necessary.

Example 3: Synthesis of N-(4-Chloro-phenyl)-2,2-dimethyl-propionamide



[00142] To a solution of 4-chloroaniline (5.0 g, 39.2 mmol) in 25 mL pyridine was added 5.3 mL (43.1 mmol) of pivaloyl chloride and the reaction mixture stirred overnight at room temperature. The mixture was poured into vigorously stirring 6M HCl, and the solids were collected by vacuum filtration, washed well with H_2O, and dried *in vacuo* to yield the title compound. 1H NMR (CDCl3) δ 7.47 (d, J = 9.2 Hz, 2H) 7.30 (s, 1H) 7.27 (d, J = 8.8 Hz, 2H) 1.32 (s, 9H) MS (ES) m/z = 212.1

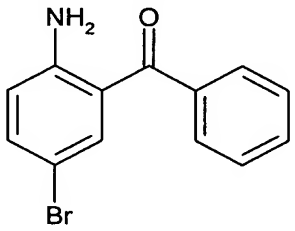
Example 4: Synthesis of (2-Amino-5-fluoro-phenyl)-phenyl-methanone



[00143] Following the general procedure for the synthesis of (2-Amino-phenyl)-aryl-methanones, a solution of BCl_3 (1M in DCM) (24 mL, 24 mmol), cooled to 0°C, was added drop wise a solution of 4-fluoroaniline (1.77 g, 16 mmol) in 30 mL of TCE over a period of 15 min and the resulting reaction mixture stirred at that temperature for an additional 10 min. Benzonitrile (2.06 g, 20 mmol) and $AlCl_3$ (3.0 g, 22mmol) were added under ice-water cooling. The solution was allowed to warm to rt and stirred for 30 min. The solution was then heated at 80-90° C for 1h and the DCM distilled off. The resulting solution was refluxed at 160° C for 4h and stirred at rt overnight. 3N HCl (20 ml approx.) was added to the reaction mixture and refluxed at 100° C for 1 hr. The reaction mixture was allowed to cool down and the solution was made basic (pH 12) with 6N NaOH. The reaction

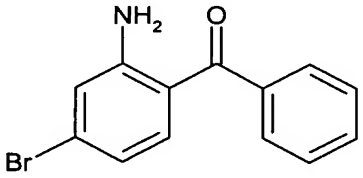
mixture was diluted with water and DCM. The resulting two layers were separated and the aqueous layer was extracted with DCM (2x150 mL) and dried over Na_2SO_4. After removal of solvent, the residue was purified by flash chromatography using ethyl acetate/hexane (1:12) as eluent. 630 mg of the pure product was obtained (yield = 18%).

Example 5: Synthesis of (2-Amino-5-bromo-phenyl)-phenyl-methanone



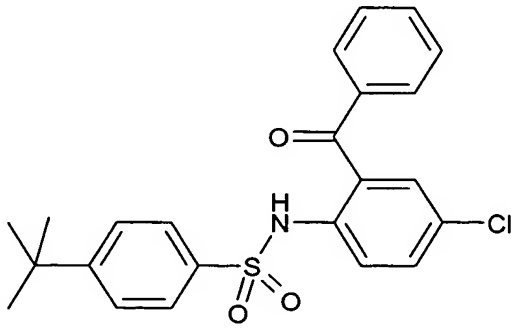
[00144] To BCl_3 (1M in DCM) (48mL, 48 mmol), cooled to 0°C, was added drop wise a solution of 4-bromoaniline (5.5 g, 32 mmol) in 60 mL of TCE over a period of 15 min and stirred at that temperature for an additional 10 min. Benzonitrile (4.12 g, 40 mmol) and $AlCl_3$ (6.0 g, 45 mmol) were added under ice-water cooling. The solution was allowed to warm to rt and stirred for 30 min. The solution was then heated at 80-90°C for 1h and the DCM distilled off. The resulting solution was refluxed at 160°C for 4h and stirred at rt overnight. 3N HCl (40 ml approx.) was added and the reaction mixture stirred at 90° C for 1 hr. The reaction mixture was allowed to cool to rt and the solution was brought to pH12 by addition of 6N aq. NaOH soln. The reaction mixture was diluted with water and DCM. The resulting two layers were separated and the aqueous layer was extracted with DCM (2x150 mL) and dried over Na_2SO_4. After removal of solvent, the residue was purified by the flash chromatography using ethyl acetate/hexane (1:12) as eluent. 1.2 g of the pure product was obtained as yellow solid (yield = 14%).

Example 6: Synthesis of (2-Amino-4-bromo-phenyl)-phenyl-methanone



[00145] To a solution of BCl_3 (1M in DCM) (31.97 mL, 32 mmol) in 20 mL of TCE, cooled in an ice-water bath, was added a solution of 3-bromoaniline (5.0 g, 29 mmol) in 20 mL of TCE drop wise over a period of 15 min and the resulting reaction mixture stirred at that temperature for an additional 15 min. Benzonitrile (6 mL, 58 mmol) and $AlCl_3$ (4.26 g, 32mmol) were added under ice-water cooling. The solution was allowed to warm to rt and stirred for 20 min. The solution was then heated at 80-90° C for 1h and the DCM distilled off. The resulting solution was refluxed at 150° C for 4h and then stirred at rt overnight. 3N HCl was added to the reaction mixture (25 mL approx.) and the reaction mixture refluxed at 90° C for 1h. The reaction mixture was allowed to cool to rt and the solution was adjusted to pH9 with 6N NaOH. The resulting two layers were separated and the basic layer was extracted with DCM (6x50 mL), dried (Na_2SO_4) and concentrated. The product was purified using column chromatography (EA: Hex, 1:9). 2.95 g of the pure product was isolated (yield = 37%). TLC analysis (EA: Hex, 1:3) Product R_f = 0.65 (yellow spot). ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.66 (dd, 1H, J = 2.5, 8 Hz), 7.11 (d, 1H, 2 Hz), 7.19 (d, 1H, 8 Hz), 7.26 (s, 2H), 7.56 (m, 5H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 197.27, 152.67, 139.49, 135.60, 131.13, 128.51, 128.27, 128.03, 118.62, 116.93, 115.44.

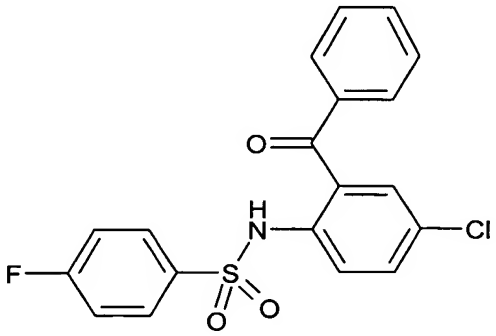
Example 7: Synthesis of N-(2-Benzoyl-4-chloro-phenyl)-4-tert-butyl-benzenesulfonamide



[00146] The title compound was prepared according to the general procedure for the synthesis of N-Aryl-benzenesulfonamides previously described using 115 mg of (2-amino-5-chloro-phenyl)-phenyl-methanone and 116 mg of 4-tert-Butyl-benzenesulfonyl chloride. ^{1}H-NMR

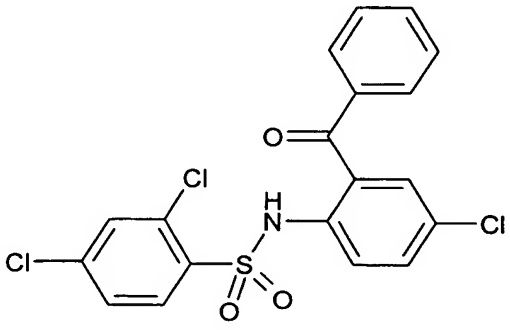
(400 MHz, $CDCl_3$): δ 1.21 (s, 9H), 7.28-7.34 (m, 3H), 7.37-7.44 (m, 4H), 7.48 (dd, 1H, J = 8.8, 2.4 Hz), 7.54-7.62 (m, 3H), 7.78 (d, 1H, J = 8.8 Hz), 9.89 (s, 1H). MS: m/z 428.9 (M^+ + 1).

Example 8: Synthesis of N-(2-Benzoyl-4-chloro-phenyl)-4-fluoro-benzenesulfonamide



[00147] The title compound was prepared according to the general procedure for the synthesis of N-Aryl-benzenesulfonamides previously described using 115 mg of (2-amino-5-chloro-phenyl)-phenyl-methanone and 87 mg of 4-fluoro-benzenesulfonyl chloride. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.90 (t, 1H, *J* = 8.8 Hz, 4.4 Hz), 7.17 (t, 1H, *J* = 7.6 Hz), 7.38-7.46 (m, 5H), 7.52 (d, 2H, *J* = 8 Hz), 7.60 (t, 1H, *J* = 7.2 Hz), 7.70 (d, 1H, *J* = 8.8 Hz), 7.83 (td, 1H, *J* = 8.4, 1.8 Hz), 10 .09 (s, 1H). MS: m/z 390.9 (M^+ + 1).

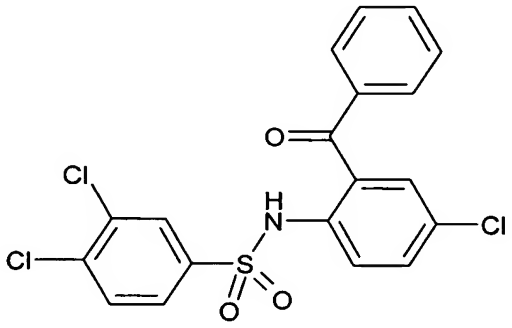
Example 9: Synthesis of N-(2-Benzoyl-4-chloro-phenyl)-2,4-dichloro-benzenesulfonamide



[00148] The title compound was prepared according to the general procedure for the synthesis of N-Aryl-benzenesulfonamides previously described using 115 mg of (2-amino-5-chloro-phenyl)-phenyl-methanone and 123 mg of 2,4-dichloro-benzenesulfonyl chloride. ^{1}H-NMR

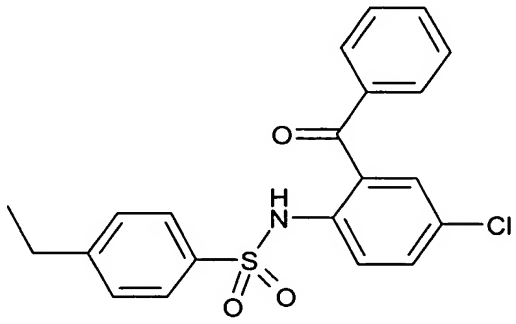
(400 MHz, $CDCl_3$): δ 7.24 (m, 1H), 7.31 (m, 1H), 7.45 (m, 2H), 7.54 (m, 2H), 7.60-7.65 (m, 2H), 7.97 (d, 1H, J = 8.4 Hz), 10.23 (s, 1H). MS: m/z 440.7 (M^+ + 1).

Example 10: Synthesis of N-(2-benzoyl-4-chloro-phenyl)-3,4-dichloro-benzenesulfonamide



[00149] The title compound was prepared according to the general procedure for the synthesis of N-Aryl-benzenesulfonamides previously described using 115 mg of (2-amino-5-chloro-phenyl)-phenyl-methanone and 123 mg of 3,4-Dichloro-benzenesulfonyl chloride. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.25 (d, 1H, J = 8.8 Hz), 7.36-39 (m, 3H), 7.43-47 (m, 3H), 7.53 (dd, 1H, J = 8.8 Hz, 2.4 Hz), 7.61 (m, 1H), 7.65 (m, 1H), 7.73 (d, 1H, J = 8.8 Hz), 9.56 (s, 1H). MS: m/z 440.7 (M^+ + 1).

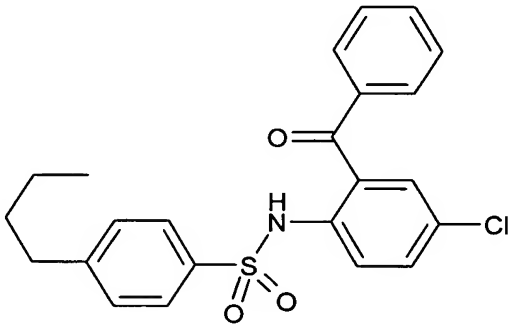
Example 11: Synthesis of N-(2-Benzoyl-4-chloro-phenyl)-4-ethyl-benzenesulfonamide



[00150] The title compound was prepared according to the general procedure for the synthesis of N-Aryl-benzenesulfonamides previously described using 115 mg of (2-amino-5-chloro-phenyl)-phenyl-methanone and 102 mg of 4-ethyl-benzenesulfonyl chloride. ^{1}H-NMR (400

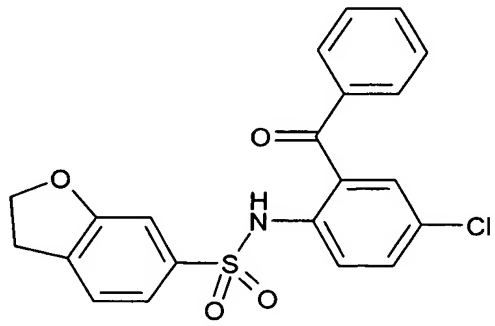
MHz, $CDCl_3$): δ 1.13 (t, 3H, J = 8.0 Hz), 2.53 (q, 2H, J – 15.3 Hz, 7.6 Hz), 7.07 (d, 2H, J = 8.4 Hz), 7.32 (d, 1H, J = 2.8 Hz), 7.34-7.42 (m, 4H), 7.48 (dd, 1H, J = 8.8 Hz, 2.4 Hz), 7.56 (m, 3H), 7.76 (d, 1H, J = 8.8 Hz), 9.75 (s, 1H). MS: m/z 400.8 (M^+ + 1).

Example 12: Synthesis of N-(2-Benzoyl-4-chloro-phenyl)-4-butyl-benzenesulfonamide



[00151] The title compound was prepared according to the general procedure for the synthesis of N-Aryl-benzenesulfonamides previously described using 115 mg of (2-amino-5-chloro-phenyl)-phenyl-methanone and 116 mg of 4-butyl-benzenesulfonyl chloride. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.90 (t, 3H, J = 6.8 Hz), 1.29 (m, 2H), 1.46 (m, 2H), 2.49 (t, 2H, J = 7.6 Hz), 7.05 (d, 2H, J = 8.4 Hz), 7.32 (d, 1H, J = 2.4 Hz), 7.40 (m. 4H), 7.47 (dd, 1H, J = 8.8 Hz, 2.8 Hz), 7.56 (m, 3H), 7.76 (d, 1H, J = 8.8 Hz), 9.78 (s, 1H). MS: m/z 428.9 (M^+ + 1).

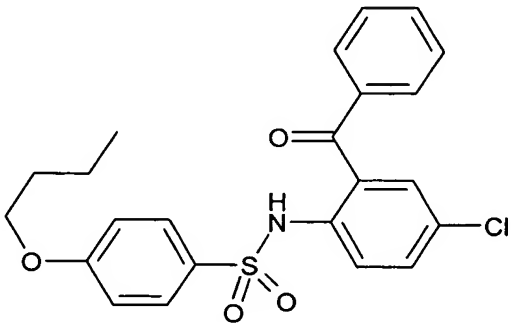
Example 13: Synthesis of 2,3-Dihydro-benzofuran-6-sulfonic acid (2-benzoyl-4-chloro-phenyl)-amide



[00152] The title compound was prepared according to the general procedure for the synthesis of N-Aryl-benzenesulfonamides

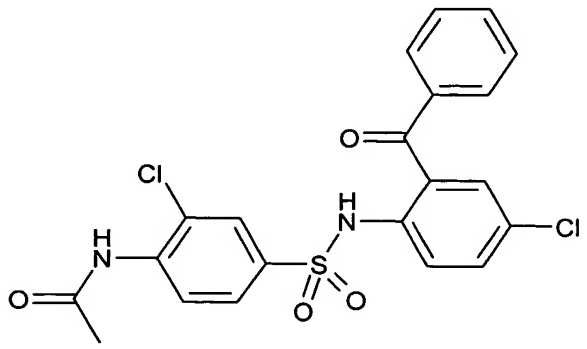
previously described using 115 mg of (2-amino-5-chloro-phenyl)-phenyl-methanone and 109 mg of 2,3-dihydro-benzofuran-6-sulfonyl chloride. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.80 (t, 2H, J = 8.8 Hz), 4.42 (t, 2H, J = 9.2 Hz), 6.57 (d, 1H, J = 8.4 Hz), 7.35 (m, 3H), 7.43 (m, 3H), 7.48 (dd, 1H, J = 8.4 Hz, 2.4 Hz), 7.6 (m, 1H), 7.74 (d, 1H, J = 8.8 Hz), 9.48 (s, 1H). MS: m/z 414.9 (M^+ + 1).

Example 14: Synthesis of N-(2-Benzoyl-4-chloro-phenyl)-4-butoxy benzenesulfonamide



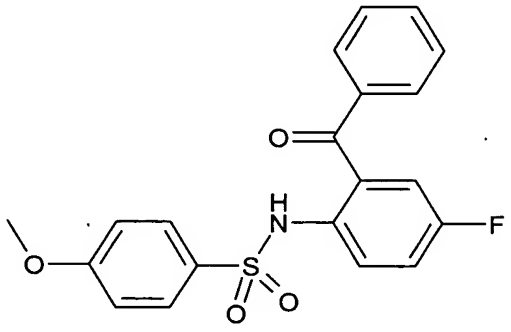
[00153] The title compound was prepared according to the general procedure for the synthesis of N-Aryl-benzenesulfonamides previously described using 115 mg of (2-amino-5-chloro-phenyl)-phenyl-methanone and 124 mg of 4-butoxy-benzenesulfonyl chloride. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.98 (t, 3H, J = 7.6 Hz), 1.45 (m, 2H), 1.72 (m, 2H), 3.79 (t, 2H, J = 6.6 Hz), 6.66 (d, 2H, J = 8.8 Hz), 7.31 (d, 1H, J = 2.8 Hz), 7.35-7.42 (m, 4H), 7.47 (dd, 1H, J = 8.8 Hz, 2.8 Hz), 7.53-7.60 (m, 3H), 7.75 (d, 1H, J = 8.8 Hz), 9.62 (s, 1H). MS: m/z 444.9 (M^+ + 1).

Example 15: Synthesis of N-[4-(2-Benzoyl-4-chloro-phenylsulfamoyl)-2-chloro-phenyl]-acetamide



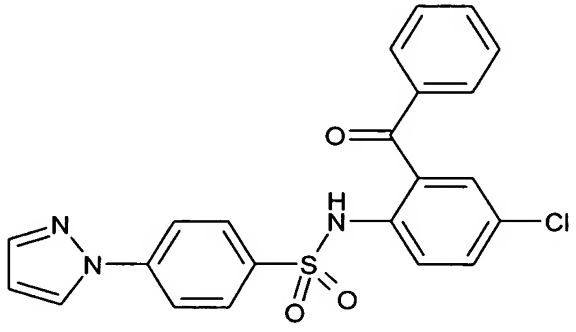
[00154] The title compound was prepared according to the general procedure for the synthesis of N-Aryl-benzenesulfonamides previously described using 115 mg of (2-amino-5-chloro-phenyl)-phenyl-methanone and 133 mg of 4-acetylamino-3-chloro-benzenesulfonyl chloride ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.24 (s, 3H), 7.36 (d, 1H, J = 2.4), 7.40-7.60(m, 8H), 7.66 (d, 1H, J = 2.0 Hz), 7.71 (d, 1H, J = 8.8 Hz), 8.36 (d, 1H, J = 8.8 Hz), 9.63 (s, 1H). MS: m/z 463.0 (M^+ + 1).

Example 16: Synthesis of N-(2-Benzoyl-4-fluoro-phenyl)-4-methoxy-benzenesulfonamide



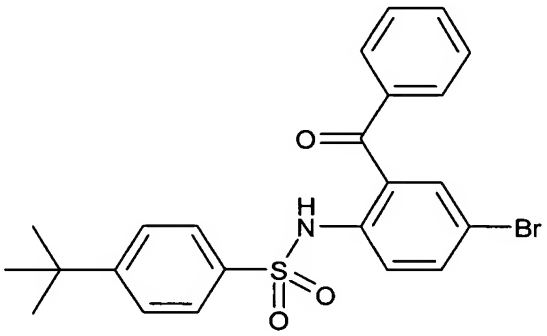
[00155] The title compound was prepared according to the general procedure for the synthesis of N-Aryl-benzenesulfonamides previously described using 115 mg of (2-amino-5-fluoro-phenyl)-phenyl-methanone and 101 mg of 4-methoxy-benzenesulfonyl chloride. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.64 (s, 3H), 6.62 (d, 2H, J = 9.2 Hz), 7.02 (m, 1H), 7.25 (m, 1H), 7.31 (m, 2H), 7.37 (m, 2H), 7.48 (m, 2H), 7.56 (m, 1H), 7.79 (q, 1H, J = 9.2 Hz, 4.8 Hz), 9.34 (s, 1H). MS: m/z 386.0 (M^+ + 1).

Example 17: Synthesis of N-(2-Benzoyl-4-chloro-phenyl)-4-pyrazol-1-yl-benzenesulfonamide



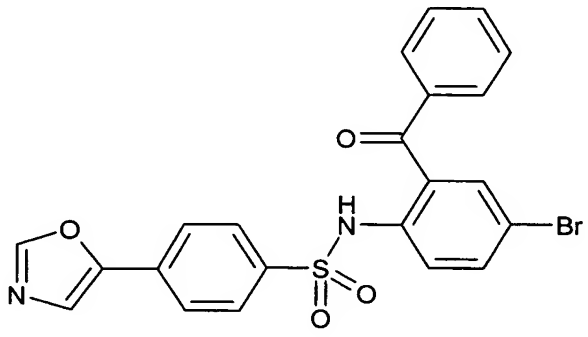
[00156] The title compound was prepared according to the general procedure for the synthesis of N-Aryl-benzenesulfonamides previously described using 116 mg of (2-Amino-5-chloro-phenyl)-phenyl-methanone and 121 mg of 4-Pyrazol-1-yl-benzenesulfonyl chloride. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.47 (m, 1H), 7.25 (m, 2H), 7.30-7.35 (m, 3H), 7.41 (m, 1H), 7.49-7.55 (m, 3H), 7.67-7.72 (m, 3H), 7.75-7.78 (m, 2H), 9.62 (s, 1H). MS: m/z 438.9 (M^+ + 1).

Example 18: Synthesis of N-(2-Benzoyl-4-bromo-phenyl)-4-tert-butyl-benzenesulfonamide



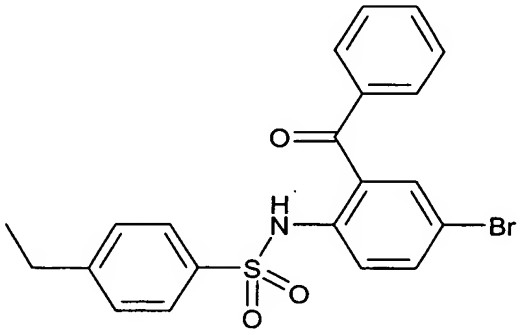
[00157] The title compound was prepared according to the general procedure for the synthesis of N-Aryl-benzenesulfonamides previously described using 138 mg of (2-Amino-5-bromo-phenyl)-phenyl-methanone and 116 mg of 4-tert-butyl-benzenesulfonyl chloride ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.21 (s, 9H), 7.30 (d, 2H, J = 8.8 Hz), 7.36-7.44 (m, 4H), 7.47 (d, 1H, J = 2.4 Hz), 7.54-7.63 (m, 4H), 7.21 (d, 1H, J = 8.8 Hz), 9.92 (s, 1H). MS: m/z 473.4 (M^+ + 1).

Example 19: Synthesis of N-(2-Benzoyl-4-bromo-phenyl)-4-oxazol-5-yl-benzenesulfonamide



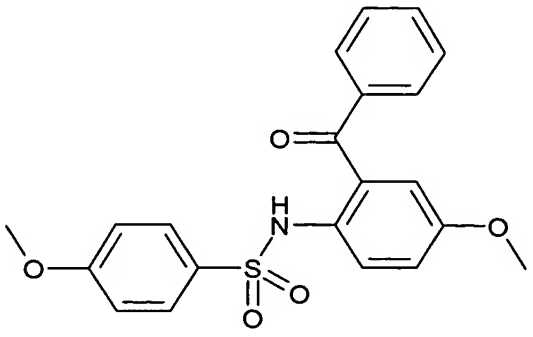
[00158] The title compound was prepared according to the general procedure for the synthesis of N-Aryl-benzenesulfonamides previously described using 138 mg of (2-amino-5-bromo-phenyl)-phenyl-methanone and 121 mg of 4-oxazol-5-yl-benzenesulfonyl chloride. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.25-7.35 (m, 5H), 7.45-7.49 (m, 4H), 7.63-7.71 (m, 4H), 7.95 (s, 1H), 9.67 (s, 1H). MS: m/z 484.3 (M^+ + 1).

Example 20: Synthesis of N-(2-Benzoyl-4-bromo-phenyl)-4-ethyl-benzenesulfonamide



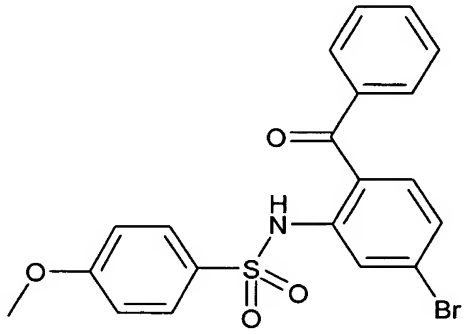
[00159] The title compound was prepared according to the general procedure for the synthesis of N-Aryl-benzenesulfonamides previously described using 138 mg of (2-amino-5-bromo-phenyl)-phenyl-methanone and 102 mg of 4-Ethyl-benzenesulfonyl chloride. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.13 (t, 3H, J = 7.6 Hz), 2.54 (q, 2H, 14.8 Hz, 7.6 Hz), 7.08 (d, 2H, J = 8.8 Hz), 7.35-7.43 (m, 4H), 7.46 (d, 1H, J = 2.4 Hz), 7.55-7.63 (m, 4H), 7.69 (d, 1H, J = 8.8 Hz), 9.78 (s, 1H). m/z 445.3 (M^+ + 1).

Example 21: Synthesis of N-(2-Benzoyl-4-methoxy-phenyl)-4-methoxy-benzenesulfonamide



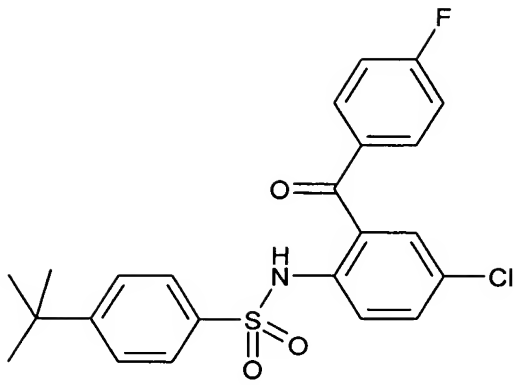
[00160] The title compound was prepared according to the general procedure for the synthesis of N-Aryl-benzenesulfonamides previously described using 115 mg of (2-Amino-5-methoxy-phenyl)-phenyl-methanone and 103 mg of 4-Methoxy-benzenesulfonyl chloride. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.60 (s, 3H), 3.72 (s, 3H), 6.55 (d, 2H, J = 8.8 Hz), 6.78 (d, 1H, J = 2.8 Hz), 7.07 (dd, 1H, J = 8.8 Hz, 2.8 Hz), 7.28- 7.37 (m, 4H), 7.42 (d, 2H, J = 6.8 Hz), 7.54 (m, 1H), 7.72 (d, 1H, J = 8.8 Hz), 9.05 (s, 1H). MS: m/z 398.3 (M^+ + 1).

Example 22: Synthesis of N-(2-Benzoyl-5-bromo-phenyl)-4-methoxy-benzenesulfonamide



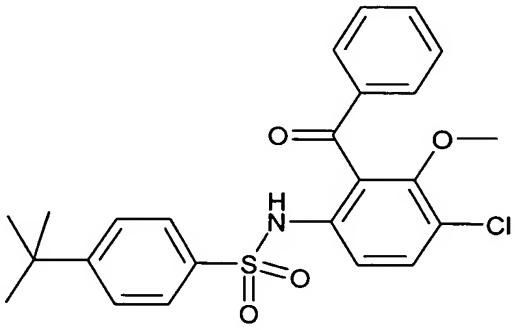
[00161] The title compound was prepared according to the general procedure for the synthesis of N-Aryl-benzenesulfonamides previously described using 138 mg of (2-Amino-4-bromo-phenyl)-phenyl-methanone and 103 mg of 4-Methoxy-benzenesulfonyl chloride. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.72 (s, 3H), 6.75 (d, 2H, J = 8.8 Hz), 7.19-7.26 (m, 2H), 7.37-7.43 (m, 4H), 7.57 (m, 1H), 7.65 (d, 2H, J = 8.8 Hz), 7.96 (s, 1H), 10.09 (s, 1H). MS: m/z 447.9 (M^+ + 1).

Example 23: Synthesis of 4-tert-Butyl-N-[4-chloro-2-(4-fluoro-benzoyl)-phenyl]-benzenesulfonamide



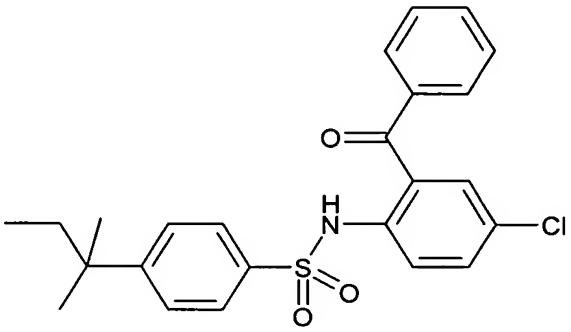
[00162] The title compound was prepared according to the general procedure for the synthesis of N-Aryl-benzenesulfonamides previously desribed using 125 mg of (2-Amino-5-chloro-phenyl)-(4-fluoro-phenyl)-methanone and 116 mg of 4-tert-butyl-benzenesulfonyl chloride. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.21 (s, 9H), 7.09 (t, 2H, J = 8.8 Hz), 7.29 (m, 3H), 7.43-7.50 (m, 3H), 7.59 (m, 2H), 7.77 (d, 1H, J = 8.8 Hz), 9.72 (s, 1H). MS: m/z 446.0 (M^+ + 1).

Example 24: Synthesis of N-(2-Benzoyl-4-chloro-3-methoxy-phenyl)-4-tert-butyl-benzenesulfonamide



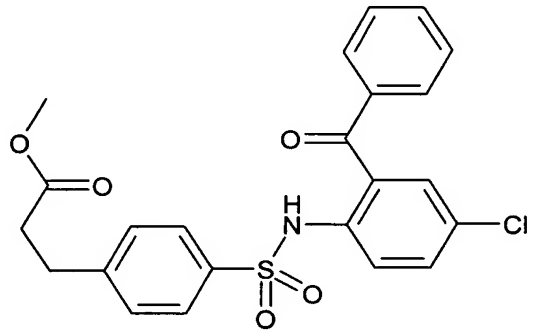
[00163] The title compound was prepared according to the general procedure for the synthesis of N-Aryl-benzenesulfonamides previously described using 131 mg of ((6-Amino-3-chloro-2-methoxy-phenyl)-phenyl-methanone and 116 mg of 4-tert-butyl-benzenesulfonyl chloride. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.23 (s, 9H), 3.74 (s, 3H), 6.73 (d, 1H, J = 2.8 Hz), 7.16 (dd, 1H, J = 9.2 Hz, 3.2 Hz), 7.33 (d, 2H, J = 8.4 Hz), 7.50 (d, 2H, J = 6.0 Hz), 7.56 (d, 2H, J = 8.8 Hz), 7.68 (d, 1H, J = 9.2 Hz), 8.82 (d, 2H, J = 6.4 Hz), 9.38 (s, 1H). MS: m/z 458.1 (M^+ + 1).

Example 25: Synthesis of N-(2-Benzoyl-4-chloro-phenyl)-4-(1,1-dimethyl-propyl)-benzenesulfonamide



[00164] The title compound was prepared according to the general procedure for the synthesis of N-Aryl-benzenesulfonamides previously described using 116 mg of (2-Amino-5-chloro-phenyl)-phenyl-methanone and 123 mg of 4-(1,1-dimethyl-propyl)-benzenesulfonyl chloride. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.56 (t, 3H, J = 7.2 Hz), 1.18 (s, 6H), 1.54 (q, 2H, J = 7.2 Hz), 7.25 (d, 2H, J = 8.4 Hz), 7.34 (d, 1H, J = 2.8 Hz), 7.40 (m, 4H), 7.45 (dd, 1H, J = 8.8 Hz, 2.0 Hz), 7.56-7.62 (m, 3H, 7.78 (d, 1H, J = 8.8 Hz), 9.95 (s, 1H). MS: m/z 442.0 (M^+ + 1).

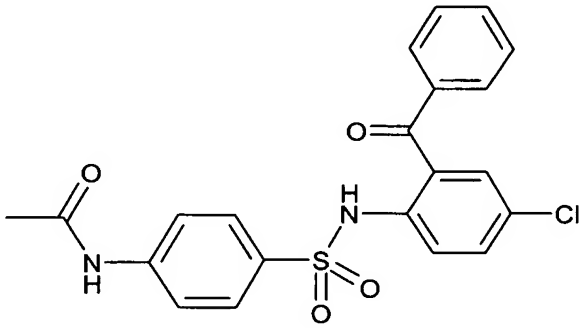
Example 26: Synthesis of 3-[4-(2-Benzoyl-4-chloro-phenylsulfamoyl)-phenyl]-propionic acid methyl ester



[00165] The title compound was prepared according to the general procedure for the synthesis of N-Aryl-benzenesulfonamides previously described using 116 mg of (2-Amino-5-chloro-phenyl)-phenyl-methanone and 131 mg of 3-(4-chlorosulfonyl-phenyl)-propionic acid methyl ester. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.50 (t, 2H, J = 8.0 Hz), 2.83 (t, 2H, J = 8.0 Hz), 3.64 (s, 3H), 7.08 (d, 2H, J = 8.8 Hz), 7.33 (d, 1H, J = 2.8 Hz), 7.36-

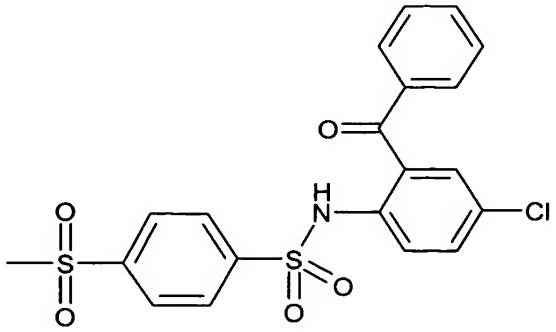
7.42 (m, 4H), 7.47 (dd, 1H, J = 8.8 Hz, 2.8 Hz), 7.58 (m, 3H), 7.75 (d, 1H, J = 8.8 Hz), 9.78 (s, 1H). MS: m/z 458.9 (M^+ + 1).

Example 27: Synthesis of N-[4-(2-Benzoyl-4-chloro-phenylsulfamoyl)-phenyl]-acetamide



[00166] The title compound was prepared according to the general procedure for the synthesis of N-Aryl-benzenesulfonamides previously described using 115 mg of (2-amino-5-chloro-phenyl)-phenyl-methanone and 117 mg of 4-Acetylamino-benzenesulfonyl chloride. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.16 (s, 3H), 7.26 (b, 1H), 7.33 (d, 1H, J = 2.4 Hz), 7.39 (m, 6H), 7.46 (dd, 1H, J = 8.4 Hz, 2.4 Hz), 7.55 (m, 3H), 7.71 (d, 1H, J = 8.8 Hz), 9.74 (s, 1H). MS: m/z 429.0 (M^+ + 1).

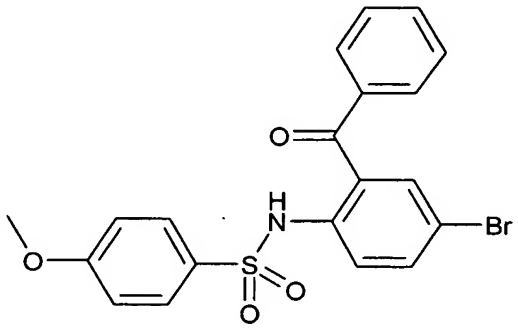
Example 28: Synthesis of N-(2-Benzoyl-4-chloro-phenyl)-4-methanesulfonyl-benzenesulfonamide



[00167] The title compound was prepared according to the general procedure for the synthesis of N-Aryl-benzenesulfonamides previously described using 115 mg of (2-amino-5-chloro-phenyl)-phenyl-methanone and 127 mg of 4-Methanesulfonyl-benzenesulfonyl chloride. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.92 (s, 3H), 7.34 (m, 3H), 7.434 (m, 2H), 7.51 (dd,

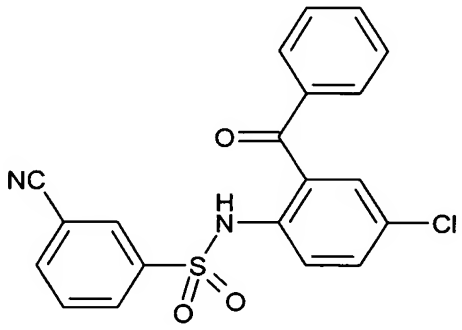
1H, J = 8.8 Hz, 2.4 Hz), 7.60 (m, 1H), 7.75 (d, 1H, J = 8.8 Hz), 7.80-7.86 (m, 4H), 9.86 (b, 1H). MS: m/z 450.9 (M^+ + 1).

Example 29: Synthesis of N-(2-Benzoyl-4-bromo-phenyl)-4-methoxy-benzenesulfonamide



[00168] The title compound was prepared according to the general procedure for the synthesis of N-Aryl-benzenesulfonamides previously described using 138 mg of (2-Amino-5-bromo-phenyl)-phenyl-methanone and 103 mg of 4-Methoxy-benzenesulfonyl chloride. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.78 (s, 3H), 6.83 (d, 2H, J = 9.2 Hz), 7.39 (b, 1H), 7.49 (d, 2H, J = 6.4 Hz), 7.68 (m, 4H), 8.85 (d, 2H, J = 6.0 Hz), 9.96 (b, 1H). MS: m/z 447.0 (M^+ + 1).

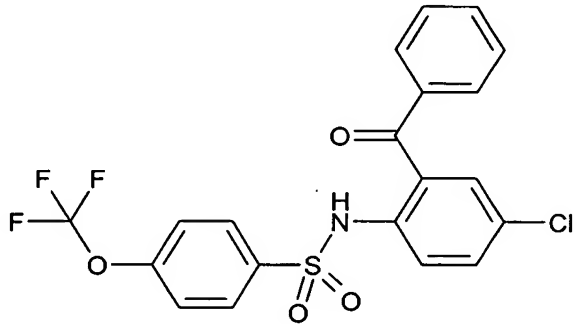
Example 30: Synthesis of N-(2-Benzoyl-4-chloro-phenyl)-3-cyano-benzenesulfonamide



[00169] The title compound was prepared according to the general procedure for the synthesis of N-Aryl-benzenesulfonamides previously described using (2-amino-5-chloro-phenyl)-phenyl-methanone and 3-Cyano-benzenesulfonyl chloride. ^{1}H NMR ($CDCl_3$): δ 7.39-7.45 (m, 6H),

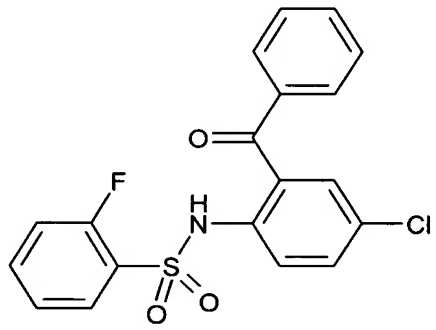
7.53-7.62 (m, 3H), 7.43 (d, J = 8.4 Hz, 1H), 7.91 (bs, 2H), 9.77 (s, 1H). MS: m/z 396.9 (M^+ + 1).

Example 31: Synthesis of N-(2-Benzoyl-4-chloro-phenyl)-4-trifluoromethoxy-benzenesulfonamide



[00170] The title compound was prepared according to the general procedure for the synthesis of N-Aryl-benzenesulfonamides previously described using (2-amino-5-chloro-phenyl)-phenyl-methanone and 4-Trifluoromethoxy-benzenesulfonyl chloride. ^{1}H NMR ($CDCl_3$): δ 7.06 (d, J = 8.0 Hz, 2H), 7.36 (m, 3H), 7.40-7.44 (m, 2H), 7.49 & 7.52 (dd, J = 8.8 Hz, 2.0 Hz, 1H), 7.58-7.62 (m, 1H), 7.70 (d, J = 8.8 Hz, 2H), 7.70 (d, J = 8.8 Hz, 1H), 9.81 (s, 1H). MS: m/z 456.0 (M^+ + 1).

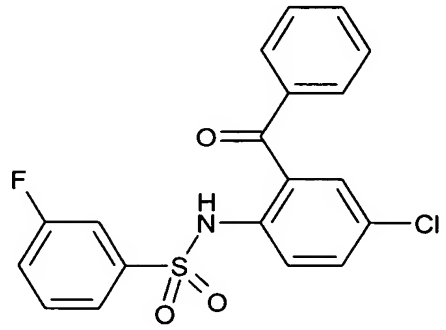
Example 32: Synthesis of N-(2-Benzoyl-4-chloro-phenyl)-2-fluoro-benzenesulfonamide



[00171] The title compound was prepared according to the general procedure for the synthesis of N-Aryl-benzenesulfonamides previously described using (2-amino-5-chloro-phenyl)-phenyl-methanone and 2-fluoro-benzenesulfonyl chloride. 1H NMR (CDCl3): δ (ppm): 6.88-6.93 (m, 1H), 7.16-7.20 (m, 1H), 7.38 (d, J = 6.4 Hz, 1H), 7.41-7.46 (m, 4H), 7.52 (m,

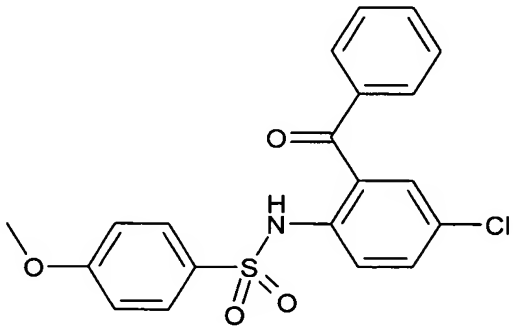
2H), 7.58-7.62 (m, 1H), 7.70 (d, J = 8.8 Hz, 1H), 7.81-7.85 (m, 1H), 10.10 (s, 1H). MS: m/z 390.0 (M^+ + 1).

Example 33: Synthesis of N-(2-Benzoyl-4-chloro-phenyl)-3-fluoro-benzenesulfonamide



[00172] The title compound was prepared according to the general procedure for the synthesis of N-Aryl-benzenesulfonamides previously described using (2-amino-5-chloro-phenyl)-phenyl-methanone and 3-fluoro-benzenesulfonyl chloride. ^{1}H NMR ($CDCl_3$): δ (ppm): 7.00-7.05 (m, 1H), 7.35 (m, 1H), 7.37 (m, 1H), 7.39-7.44 (m, 4H), 7.37-7.43 (m, 4H), 7.45-7.46 (m, 1H), 7.49-7.50 (m, 1H), 7.51-7.52 (m, 2H), 7.58-7.62 (m, 1H), 9.80 (s, 1H). MS: m/z 390.0 (M^++1).

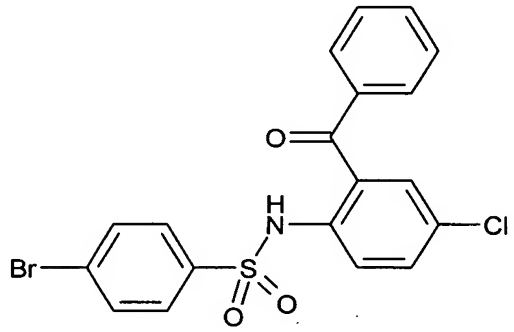
Example 34: Synthesis of N-(2-Benzoyl-4-chloro-phenyl)-4-methoxy-benzenesulfonamide



[00173] The known compound was prepared according to the general procedure for the synthesis of N-Aryl-benzenesulfonamides previously described using (2-Amino-5-chloro-phenyl)-phenyl-methanone and 4-methoxy-benzenesulfonyl chloride and purified by flash chromatography (20% EtOAc.Hexane). ^{1}H NMR (CDCl3) δ 9.63 (s, 1H) 7.75 (d, J = 12 Hz, 1H)

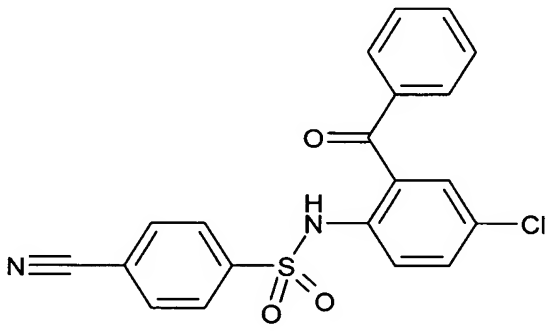
7.57 (m, 3H) 7.49- 7.35 (m, 5H) 7.33 (d, J = 4 Hz, 1H) 6.69 (d, J = 12 Hz, 2H) 3.67 (s, 3H). MS: m/z = 402.0 (M^+ + 1).

Example 35: Synthesis of N-(2-Benzoyl-4-chloro-phenyl)-4-bromo-benzenesulfonamide



[00174] 2-Amino-5-chlorobenzophenone (5.33 g, 23 mmol) was dissolved in 100 mL pyridine and stirred at room temperature. 4-Bromobenzenesulfonyl chloride (6.17 g, 24.1 mmol) was added and the mixture was stirred overnight. The mixture was poured in a steady stream into 350 mL vigorously stirring chilled 6M HCl which resulted in the precipitation of a reddish oil. The solution was diluted with 100mL EtOAc and 200 mL H_2O, shaken in a separating funnel and the aqueous layer discarded. The organics were dried and reduced *in vacuo* to yield title compound (10.2 g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (m, 5H), 7.43-7.48 (m, 5H), 7.62 (t, 1H), 7.74 (d, 1H), 9.62 (s, 1H). MS: m/z = 449.9 (M^+ + 1).

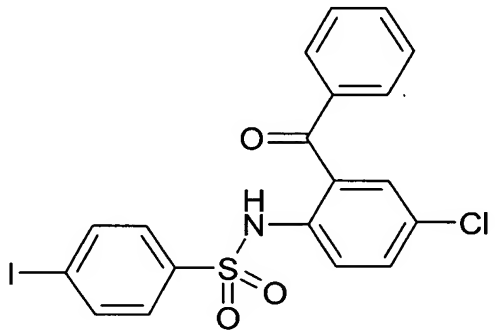
Example 36: Synthesis of N-(2-Benzoyl-4-chloro-phenyl)-4-cyano-benzenesulfonamide



[00175] 2-Amino-5-chlorobenzophenone (2.92 g, 12.60 mmol) was dissolved in 60 mL of pyridine and 4-cyanobenzenesulfonyl chloride (2.66

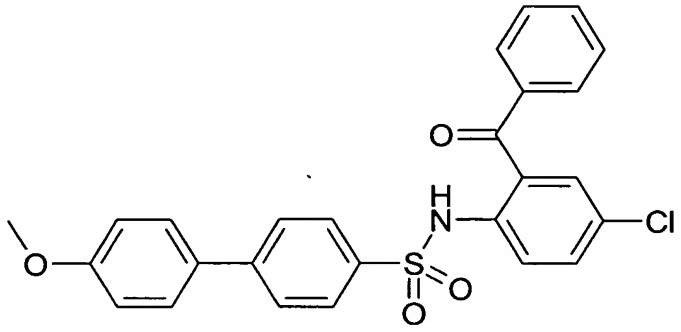
g, 13.2 mmol) in 10 mL pyridine was then added. The mixture was stirred overnight at room temperature under N2, then poured in a steady stream into 350 mL vigorously stirring chilled 6M HCl which resulted in the precipitation of a yellow solid which was collected by vacuum filtration, washed well with H_2O, then dissolved in 50 mL EtOAc and the solvents removed under vacuum to get a reddish powder which was dissolved in 75 mL boiling acetone. 150 mL of H_2O was added in a slow stream to the hot, stirring acetone solution. A yellow precipitate formed upon cooling which was collected by vacuum filtration and dried overnight under vacuum to get 5.7g product as a reddish powder (quant). 1H NMR (DMSO) δ 10.28 (s, 1H) 7.92 (dd, J = 1.6, 8.8, 2H) 7.70 (d, 2H) 7.64(t, 1H) 7.58- 7.52 (m, 3H) 7.50- 7.46 (m, 2H) 7.42 (d, J = 2.8 Hz, 1H) 7.03 (d, 8.8 Hz, 1H). MS: m/z = 397.0 (M^+ + 1).

Example 37: Synthesis of N-(2-Benzoyl-4-chloro-phenyl)-4-iodo-benzenesulfonamide



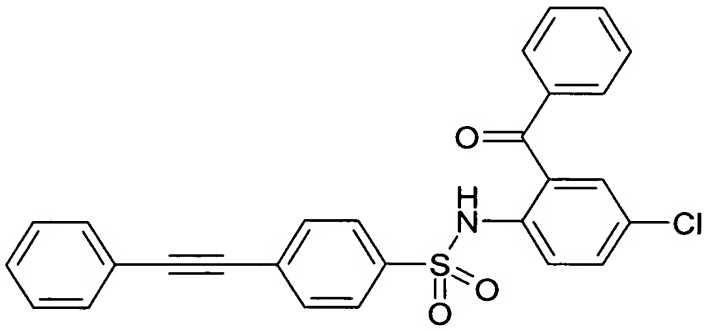
[00176] To a magnetically stirred solution of 2-amino-5-chlorobenzophenone (1.62 g, 7.0 mmol) in dry pyridine (30 mL) was added drop wise a solution of pipsyl chloride in toluene (12 mL) and the reaction was stirred at ambient temperature. The reaction was added to cold (ice bath) 6M hydrochloric acid with stirring and the mixture was extracted with ethyl acetate (3 x 50 mL). The extracts were washed with water and with saturated aqueous NaCl. The organic layer was dried (MgSO4), filtered and concentrated to give a crystalline solid. The product was filtered, washed with hexane and dried (vacuum) to get white crystalline solid. ^{1}H NMR (CDCl3) δ 9.63 (br s, 1H, NH), 7.75 (dm, 1H, J = 8.8 Hz), 7.62 (tm, 1H, J = 7.6 Hz), 7.56 (dm, 1H, J = 7.6 Hz), 7.48 (m, 3H), 7.32 (m, 5H). MS: m/z 498.0 (M +1).

Example 38: Synthesis of 4'-Methoxy-biphenyl-4-sulfonic acid (2-benzoyl-4-chloro-phenyl)-amide



[00177] To a magnetically stirred mixture of N-(2-Benzoyl-4-chloro-phenyl)-4-iodo-benzenesulfonamide (497 mg, 1.0 mmol), [1,1' Bis(diphenylphosphino)-ferrocene]dichloropalladium(II) complex with dichloromethane (1:1) (30 mg, 0.037 mmol) and dry cesium carbonate (511 mg, 1.57 mmol) in NMP (3 mL), was added DME (3 mL) and dry triethylamine (3 mL) under dry nitrogen. To this stirred mixture was added (4-methoxyphenyl)boronic acid (202 mg) and the mixture was stirred at 55°C overnight. The reaction was worked up by addition to crushed ice and extracted with ethyl acetate (3 X 75 mL), and the organic layer was dried ($MgSO_4$), filtered and concentrated. The crude product was chromatographed on silica gel using 10-30% EtOAc/Hexane. ^1H NMR (CDCl3) δ 9.64 (br s, 1H, NH), 7.75 (dm, 1H), 7.75 (dm, 2H, J = 8.8 Hz), 7.48 (m, 3H), 7.56 (dm, 2H, J = 8.4 Hz), 7.51 (m), 7.32 (d 1H, J = 2.2 Hz), 7.26 (d, 1H, J = 7 Hz), 7.09 (d, 2H, J = 8.4 Hz), 3.65 (s, 3H). MS: m/z 478.0 (M +1).

Example 39: Synthesis of N-(2-Benzoyl-4-chloro-phenyl)-4-phenylethynyl-benzenesulfonamide



[00178] To a magnetically stirred mixture of the N-(2-Benzoyl-4-chloro-phenyl)-4-bromo-benzenesulfonamide (450 mg, 1.0 mmol), [1,1' Bis-(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (1:1) (30 mg, 0.037 mmol) and copper (I) iodide (100 mg, 0.52 mmol) was added DME (6 mL) and dry triethylamine (3 mL) under dry nitrogen. To this stirred mixture was added tetrabutylammonium iodide (250 mg), followed by the addition of phenylacetylene (0.240 mL). The dark green mixture was stirred at ambient temp overnight. The reaction was worked up by addition to crushed ice and extracted with ethyl acetate (3 X 75 mL), and the organic layer was dried ($MgSO_4$), filtered and concentrated. The crude product was chromatographed on silica gel using 10-30% EtOAc/Hexane. ^1H NMR (CDCl3) δ 9.64 (br s, 1H, NH), 7.75 (d, 1H, J = Hz), 7.75 (d, 1H, J = 8.8 Hz), 7.48 (m, 8H), 7.36 (m, 7H). MS: m/z 472 (M + 1)

Measuring efficacy of CCR9 modulators

In vitro assays

[00179] A variety of assays can be used to evaluate the compounds provided herein, including signaling assays, migration assays, and other assays of cellular response. CCR9 receptor signaling assays can be used to measure the ability of a compound, such as a potential CCR9 antagonist, to block CCR9 ligand- (e.g. TECK)-induced signaling. A migration assay can be used to measure the ability of a compound of interest, such as a possible CCR9 antagonist, to block CCR9-mediated cell migration in vitro. The latter is believed to resemble chemokine-induced cell migration in vivo.

[00180] In a suitable assay, a CCR9 protein (whether isolated or recombinant) is used which has at least one property, activity, or functional characteristic of a mammalian CCR9 protein. The property can be a binding property (to, for example, a ligand or inhibitor), a signaling activity (e.g., activation of a mammalian G protein, induction of rapid and transient increase in the concentration of cytosolic free calcium [Ca^{++}]), cellular response function (e.g., stimulation of chemotaxis or inflammatory mediator release by leukocytes), and the like.

[00181] The assay can be a cell based assay that utilizes cells stably or transiently transfected with a vector or expression cassette having a nucleic acid sequence which encodes the CCR9 receptor. The cells are maintained under conditions appropriate for expression of the receptor and are contacted with a putative agent under conditions appropriate for binding to occur. Binding can be detected using standard techniques. For example, the extent of binding can be determined relative to a suitable control (for example, relative to background in the absence of a putative agent, or relative to a known ligand). Optionally, a cellular fraction, such as a membrane fraction, containing the receptor can be used in lieu of whole cells.

[00182] Detection of binding or complex formation can be detected directly or indirectly. For example, the putative agent can be labeled with a suitable label (e.g., fluorescent label, chemiluminescent label, isotope label, enzyme label, and the like) and binding can be determined by detection of the label. Specific and/or competitive binding can be assessed by competition or displacement studies, using unlabeled agent or a ligand (e.g., TECK) as a competitor.

[00183] Binding inhibition assays can be used to evaluate the present compounds. In these assays, the compounds are evaluated as inhibitors of ligand binding using, for example, TECK. In this embodiment, the CCR9 receptor is contacted with a ligand such as TECK and a measure of ligand binding is made. The receptor is then contacted with a test agent in the presence of a ligand (e.g., TECK) and a second measurement of binding is made. A reduction in the extent of ligand binding is indicative of inhibition of binding by the test agent. The binding inhibition assays can be carried out using whole cells which express CCR9, or a membrane fraction from cells which express CCR9.

[00184] The binding of a G protein coupled receptor by, for example, an agonist, can result in a signaling event by the receptor. Accordingly, signaling assays can also be used to evaluate the compounds of the present invention and induction of signaling function by an agent can be monitored using any suitable method. For example, G protein activity, such

as hydrolysis of GTP to GDP, or later signaling events triggered by receptor binding can be assayed by known methods (see, for example, PCT/US97/15915; Neote, *et al.*, *Cell*, 72:415425 (1993); Van Riper, *et al.*, *J. Exp. Med.*, 177:851-856 (1993) and Dahinden, *et al.*, *J. Exp. Med.*, 179:751-756 (1994)).

[00185] Chemotaxis assays can also be used to assess receptor function and evaluate the compounds provided herein. These assays are based on the functional migration of cells in vitro or in vivo induced by an agent, and can be used to assess the binding and/or effect on chemotaxis of ligands, inhibitors, or agonists. A variety of chemotaxis assays are known in the art, and any suitable assay can be used to evaluate the compounds of the present invention. Examples of suitable assays include those described in PCT/US97/15915; Springer, *et al.*, WO 94/20142; Berman *et al.*, *Immunol. Invest.*, 17:625-677 (1988); and Kavanaugh *et al.*, *J. Immunol.*, 146:4149-4156 (1991)).

[00186] Calcium signaling assays measure calcium concentration over time, preferably before and after receptor binding. These assays can be used to quantify the generation of a receptor signaling mediator, Ca^{++}, following receptor binding (or absence thereof). These assays are useful in determining the ability of a compound, such as those of the present invention, to generate the receptor signaling mediator by binding to a receptor of interest. Also, these assays are useful in determining the ability of a compound, such as those of the present invention, to inhibit generation of the receptor signaling mediator by interfering with binding between a receptor of interest and a ligand.

[00187] In calcium signaling assays used to determine the ability of a compound to interfere with binding between CCR9 and a known CCR9 ligand, CCR9-expressing cells (such as a T cell line MOLT-4 cells) are first incubated with a compound of interest, such as a potential CCR9 antagonist, at increasing concentrations. The cell number can be from 10^5 to $5X10^5$ cells per well in a 96-well microtiter plate. The concentration of the compound being tested may range from 0 to 100 μM. After a period of incubation (which

can range from 5 to 60 minutes), the treated cells are placed in a Fluorometric Imaging Plate Reader (FLIPR®) (available from Molecular Devices Corp., Sunnyvale, CA) according to the manufacturer's instruction. The FLIPR system is well known to those skilled in the art as a standard method of performing assays. The cells are then stimulated with an appropriate amount of the CCR9 ligand TECK (e.g. 5-100 nM final concentration) and the signal of intracellular calcium increase (also called calcium flux) is recorded. The efficacy of a compound as an inhibitor of binding between CCR9 and the ligand can be calculated as an IC50 (the concentration needed to cause 50% inhibition in signaling) or IC90 (at 90% inhibition).

[00188] In vitro cell migration assays can be performed (but are not limited to this format) using the 96-well microchamber (called ChemoTX™). The ChemoTX system is well known to those skilled in the art as a type of chemotactic/cell migration instrument. In this assay, CCR9-expressing cells (such as MOLT-4) are first incubated with a compound of interest, such as a possible CCR9 antagonist, at increasing concentrations. Typically, fifty thousand cells per well are used, but the amount can range from 10^3-10^6 cells per well. CCR9 ligand TECK, typically at 50 nM (but can range from 5-100 nM), is placed at the lower chamber and the migration apparatus is assembled. Twenty microliters of test compound-treated cells are then placed onto the membrane. Migration is allowed to take place at 37 C for a period of time, typically 2.5 hours. At the end of the incubation, the number of cells that migrated across the membrane into the lower chamber is then quantified. The efficacy of a compound as an inhibitor of CCR9-mediated cell migration is calculated as an IC50 (the concentration needed to reduce cell migration by 50%) or IC90 (for 90% inhibition).

In vivo efficacy models for human IBD

[00189] T cell infiltration into the small intestine and colon have been linked to the pathogenesis of human inflammatory bowel diseases which include Coeliac disease, Crohn's disease and ulcerative colitis. Blocking trafficking of relevant T cell populations to the intestine is believed to be an effective approach to treat human IBD. CCR9 is expressed on gut-homing T

cells in peripheral blood, elevated in patients with small bowel inflammation such as Crohn's disease and Coeliac disease. CCR9 ligand TECK is expressed in the small intestine. It is thus believed that this ligand-receptor pair plays a role in IBD development by mediating migration of T cells to the intestine. Several animal models exist and can be used for evaluating compounds of interest, such as potential CCR9 antagonists, for an ability to affect such T cell migration and/or condition or disease, which might allow efficacy predictions of antagonists in humans.

Animal models with pathology similar to human ulcerative colitis

[00190] A murine model described by Panwala and coworkers (Panwala, et al., *J Immunol.*, 161(10):5733-44 (1998)) involves genetic deletion of the murine multi-drug resistant gene (MDR). MDR knockout mice (MDR-/-) are susceptible to developing a severe, spontaneous intestinal inflammation when maintained under specific pathogen-free facility conditions. The intestinal inflammation seen in MDR-/- mice has a pathology similar to that of human inflammatory bowel disease (IBD) and is defined by Th1 type T cells infiltration into the lamina propria of the large intestine.

[00191] Another murine model was described by Davidson *et al., J Exp Med.*, 184(1):241-51(1986). In this model, the murine IL-10 gene was deleted and mice rendered deficient in the production of interleukin 10 (IL-10-/-). These mice develop a chronic inflammatory bowel disease (IBD) that predominates in the colon and shares histopathological features with human IBD.

[00192] Another murine model for IBD has been described by *Powrie et al., Int Immunol.,* 5(11):1461-71 (1993), in which a subset of CD4+ T cells (called CD45RB(high)) from immunocompetent mice are purified and adoptively transferred into immunodeficient mice (such as C.B-17 scid mice). The animal restored with the CD45RBhighCD4+ T cell population developed a lethal wasting disease with severe mononuclear cell infiltrates in the colon, pathologically similar with human IBD.

Murine models with pathology similar to human Crohn's disease

[00193] The TNF ARE(-/-) model. The role of TNF in Crohn's disease in human has been demonstrated more recently by success of treatment using anti-TNF alpha antibody by Targan *et al., N Engl J Med.,* 337(15):1029-35 (1997). Mice with aberrant production of TNF-alpha due to genetic alteration in the TNF gene (ARE-/-) develop Crohn's-like inflammatory bowel diseases (*see* Kontoyiannis *et al., Immunity,* 10(3):387-98 (1999)).

[00194] The SAMP/yit model. This is model described by Kosiewicz *et al., J Clin Invest.*, 107(6):695-702 (2001). The mouse strain, SAMP/Yit, spontaneously develops a chronic inflammation localized to the terminal ileum. The resulting ileitis is characterized by massive infiltration of activated T lymphocytes into the lamina propria, and bears a remarkable resemblance to human Crohn's disease.

Example 40

[00195] This example illustrates the activity associated with representative compounds of the invention.

Materials and Methods (in vitro assays)

Reagents and cells

[00196] MOLT-4 cells were obtained from the American Type Culture Collection (Manassas, VA) and cultured in RPMI tissue culture medium supplemented with 10% fetal calf serum (FCS) in a humidified 5% CO_2 incubator at 37° C. Recombinant human chemokine protein TECK was obtained from R&D Systems (Minneapolis, MN). ChemoTX® chemotaxis microchambers were purchased from Neuro Probe (Gaithersburg, MD). CyQUANT® cell proliferation kits were purchased from Molecular Probes (Eugene, Oregon). Calcium indicator dye Fluo-4 AM was purchased from Molecular Devices (Mountain View, CA).

Conventional migration assay

[00197] Conventional migration assay was used to determine the efficacy of potential receptor antagonists in blocking migration mediated

through CCR9. This assay was routinely performed using the ChemoTX® microchamber system with a 5-μm pore-sized polycarbonate membrane. To begin such an assay, MOLT-4 cells were harvested by centrifugation of cell suspension at 1000 PRM on a GS-6R Beckman centrifuge. The cell pellet was resuspended in chemotaxis buffer (HBSS with 0.1% BSA) at $5x10^6$ cells/mL. Test compounds at desired concentrations were prepared from 10 mM stock solutions by serial dilutions in chemotaxis buffer. An equal volume of cells and compounds were mixed and incubated at room temperature for 15 minutes. Afterwards, 20 μL of the mixture was transferred onto the porous membrane of a migration microchamber, with 29 μL of 50 nM chemokine TECK protein placed at the lower chamber. Following a 150-minute incubation at 37° C, during which cells migrated against the chemokine gradient, the assay was terminated by removing the cell drops from atop the filter. To quantify cells migrated across the membrane, 5 μL of 7X CyQUANT® solution was added to each well in the lower chamber, and the fluorescence signal measured on a Spectrafluor Plus fluorescence plate reader (TECAN, Durham, NC). The degree of inhibition was determined by comparing migration signals between compound-treated and untreated cells. IC50 calculation was further performed by non-linear squares regression analysis using Graphpad Prism (Graphpad Software, San Diego, CA).

RAM assay

[00198] The primary screen to identify CCR9 antagonists was carried out using RAM assay (WO 02101350), which detects potential hits by their ability to activate cell migration under inhibitory TECK concentration. To begin such an assay, MOLT-4 cells were harvested by centrifugation of cell suspension at 1000 RPM on a GS-6R Beckman centrifuge. The cell pellet was resuspended in chemotaxis buffer (HBSS/0.1% BSA) at $5x10^6$ cells/mL. Twenty-five microliters of cells was mixed with an equal volume of a test compound diluted to 20 μM in the same buffer. Twenty microliters of the mixture was transferred onto the filter in the upper chemotaxis chamber, with

29 μL of 500 nM chemokine protein TECK placed in the lower chamber. Following a 150-minute incubation at 37° C, the assay was terminated by removing the cell drops from atop the filter. To quantify cells migrated across the membrane, 5 μL of 7X CyQUANT® solution was added to each well in the lower chamber, and the fluorescence signal measured on a Spectrafluor Plus fluorescence plate reader (TECAN, Durham, NC).

[00199] For selection of potential hits, the level of migration activation was calculated as a RAM index-the ratio between the signal of a particular well and the median signal of the whole plate. Compounds with a RAM index of greater than 1.8 were regarded as RAM positive, and were selected for IC_{50} determinations in conventional functional assays.

Calcium flux assay

[00200] Calcium flux assay measures an increase in intracellular calcium following ligand-induced receptor activation. In the screen of CCR9 antagonists, it was used as a secondary assay carried out on a FLIPR® machine (Molecular Devices, Mountain View, CA). To begin an assay, MOLT-4 cells were harvested by centrifugation of cell suspension, and resuspended to $1.5x10^6$ cells/mL in HBSS (with 1% fetal calf serum). Cells were then labeled with a calcium indicator dye Fluo-4 AM for 45 minutes at 37° C with gentle shaking. Following incubation, cells were pelletted, washed once with HBSS and resuspended in the same buffer at a density of $1.6x10^6$ cells/mL. One hundred microliters of labeled cells were mixed with 10 μL of test compound at the appropriate concentrations on an assay plate. Chemokine protein TECK was added at a final concentration of 25 nM to activate the receptor. The degree of inhibition was determined by comparing calcium signals betweeen compound-treated and untreated cells. IC50 calculations were further performed by non-linear squares regression analysis using Graphpad Prism (Graphpad Software, San Diego, CA).

Discovery of CCR9 antagonists

[00201] The discovery of CCR9 antagonists was carried out in two steps: First, RAM assay was used to screen a compound library in a high-throughput manner. The assay detected compounds by their ability to cause a positive migration signal under RAM condition. Secondly, RAM positive compounds were tested to determine their IC_{50}s using the conventional migration and calcium flux assays.

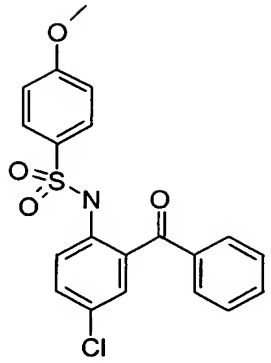
[00202] For instance, in a screen of approximately 100,000 compounds, 2000 individual wells representing approximately 2% of total compounds showed a RAM index greater than 1.8. These compounds were cheery-picked and retested in duplicate wells by RAM assay. A total of 270 compounds, or 0.27% of the library, were confirmed RAM positives.

[00203] Since a RAM positive signal indicates only the presence of a receptor antagonist and not how strongly it blocks receptor functions, the RAM positive compounds were further tested for potency in calcium flux assay using MOLT-4 cells. IC_{50} determinations on this subset discovered several compounds with IC_{50}'s less than 1 μM and that did not inhibit other chemokine receptors examined at significant levels.

In vivo efficacy studies

[00204] The MDR1α-knockout mice, which lack the P-glycoprotein gene, spontaneously develop colitis under specific pathogen-free condition. The pathology in these animals has been characterized as Th1-type T cell-mediated inflammation similar to ulcerative colitis in humans. Disease normally begins to develop at around 8-10 weeks after birth. But the ages at which disease emerges and the ultimate penetrance level often vary considerably among different animal facilities.

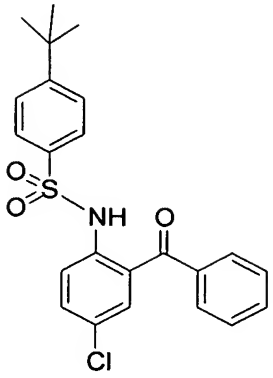
[00205] In a study using the MDR1α-knockout mice, the known compound shown below was tested for its ability to delay disease onset during a short treatment regimen.



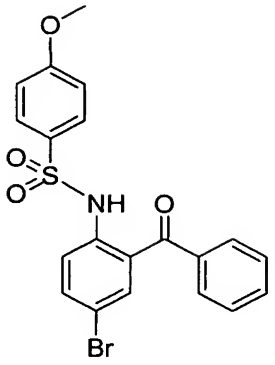
[00206] This compound is structurally similar to the claimed modulators (I) of the present invention. Female mice (n=15) were dosed with 50 mg/kg twice a day by intraperitonial injection, starting at age 13 weeks for 14 consecutive days. The study was terminated when the mice reached age 17 weeks at which point the disease penetrance level measured by diarrhea incidence reached 55%. The study showed that the compound was well tolerated; mice in the compound-treated group showed a significant delay in the onset of IBD symptoms. This protection extended one to two weeks after treatment stopped (Figure 1).

[00207] In the table below, structures and activity are provided for representative compounds described herein. Activity is provided as follows for either or both of the chemotaxis assay and/or calcium mobilization assays, described above: + 1000 nM < IC_{50} < 10000nM; ++, 100 nM < IC_{50} < 1000 nM; and +++, IC_{50} < 100 nM.

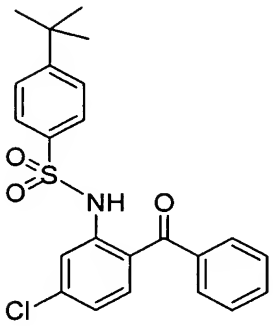
Table 1: Compounds with activity in either or both of the chemotaxis assay and calcium mobilization assays, with IC_{50} < 100 nM (+++)


O
O
S
NH
O
Cl

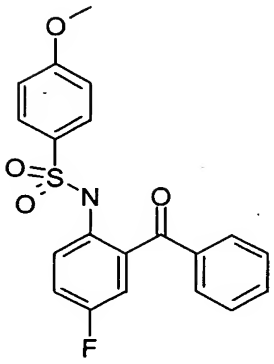
(+++)


O
O
O
S
NH
O
Br

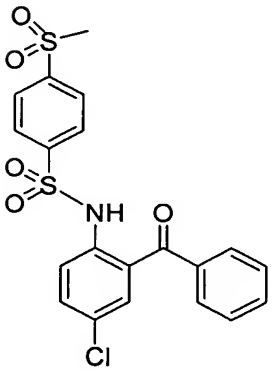
(+++)


O
O
S
NH
O
Cl

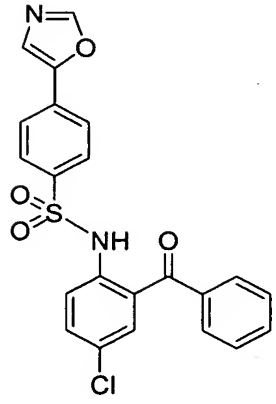
(+++)


O
O
O
S
N
O
F

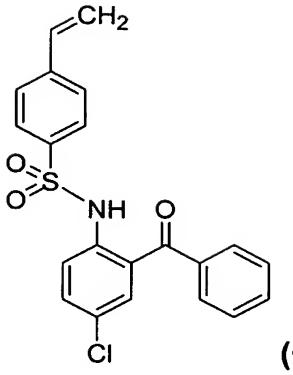
(+++)


O
O
S
O
O
S
NH
O
Cl

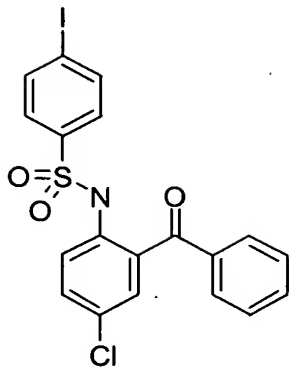
(+++)


N
O
O
O
S
NH
O
Cl

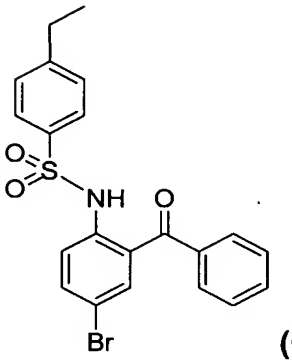
(+++)


CH2
O
S
O
NH
O
Cl

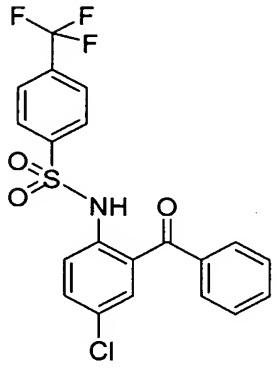
(+++)


I
O
S
O
N
O
Cl

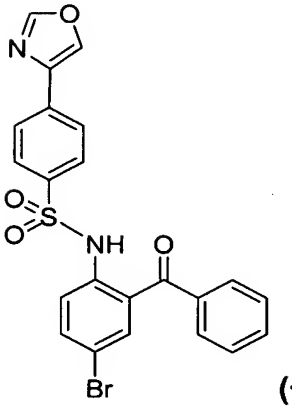
(+++)


O
S
O
NH
O
Br

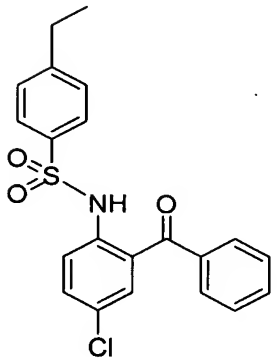
(+++)


F
F
F
O
S
O
NH
O
Cl

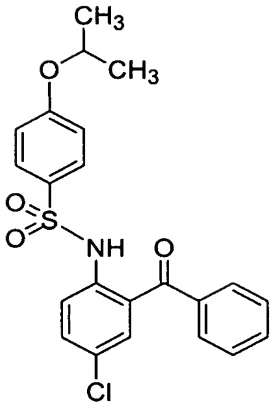
(+++)


N
O
O
S
O
NH
O
Br

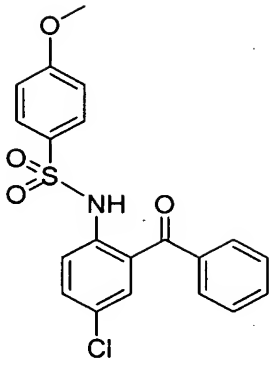
(+++)


O
S
O
NH
O
Cl

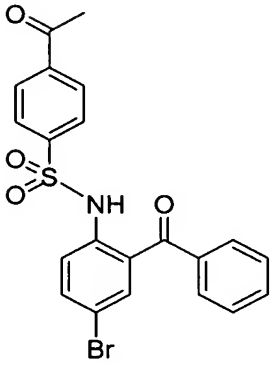
(+++)


CH3
O
CH3
O
S
O
NH
O
Cl

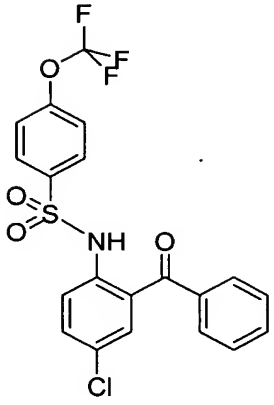
(+++)


O
O
S
O
NH
O
Cl

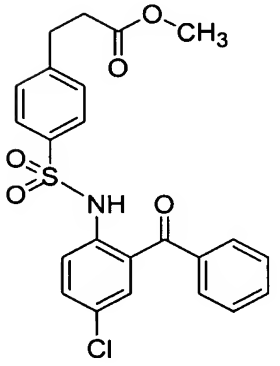
(+++)


O
O
S
O
NH
O
Br

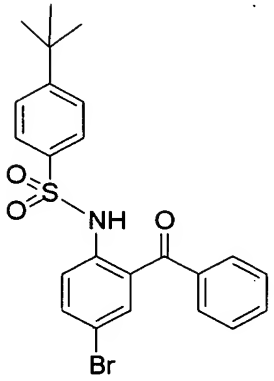
(+++)


F
F
F
O
O
S
O
NH
O
Cl

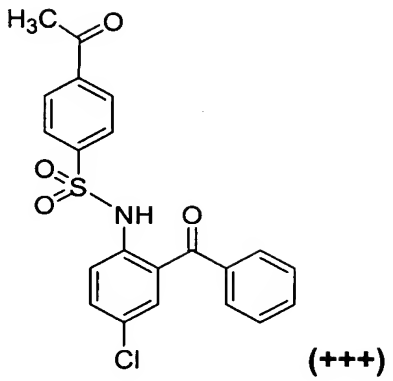
(+++)


O
CH3
O
O
S
O
NH
O
Cl

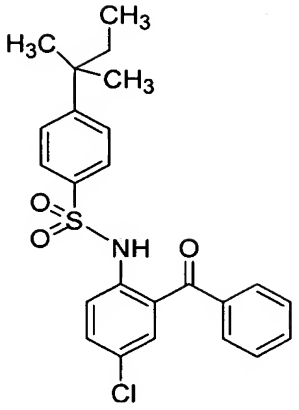
(+++)


O
S
O
NH
O
Br

(+++)

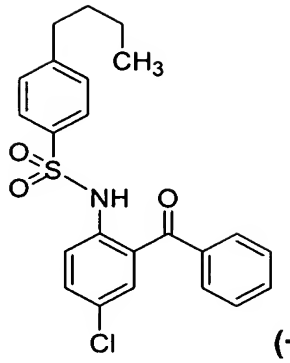


(+++)

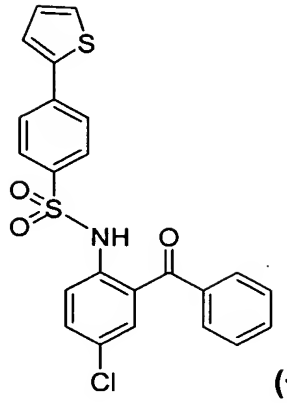


(+++)

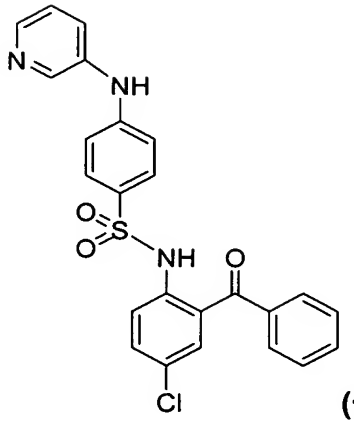
Table 2: Compounds with activity in either or both of the chemotaxis assay and calcium mobilization assays, with 100 nM < IC_{50} < 1000 nM (++)


CH3
O
S
O
NH
O
Cl

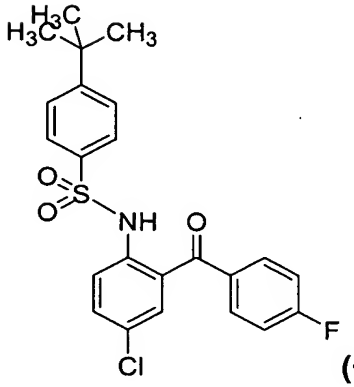
(++)


S
O
S
O
NH
O
Cl

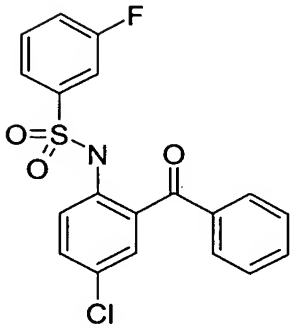
(++)


N
NH
O
S
O
NH
O
Cl

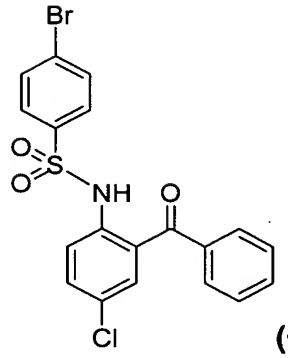
(++)


H3C
H3C
CH3
O
S
O
NH
O
F
Cl

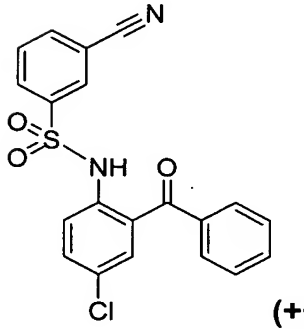
(++)


F
O
S
O
N
O
Cl

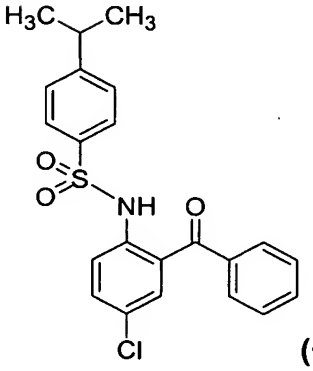
(++)


Br
O
S
O
NH
O
Cl

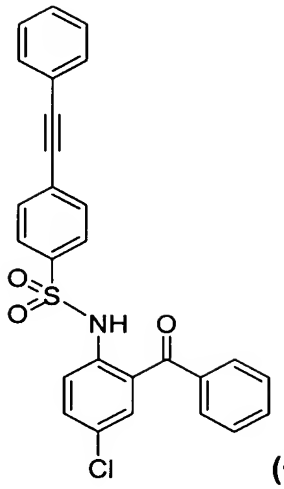
(++)


N
O
S
O
NH
O
Cl

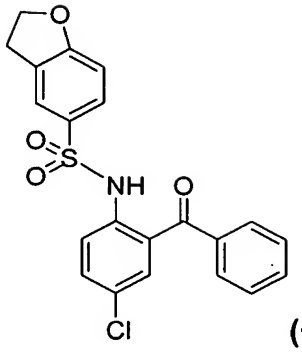
(++)


H3C
CH3
O
S
O
NH
O
Cl

(++)



(++)



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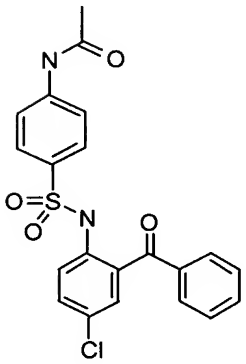
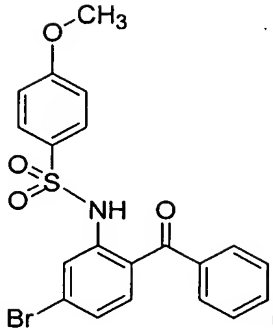
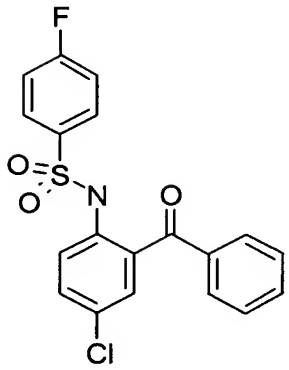


(++)



(++)



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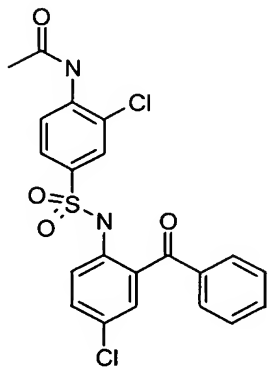

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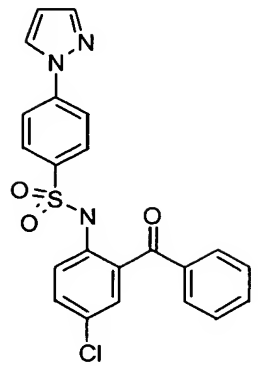

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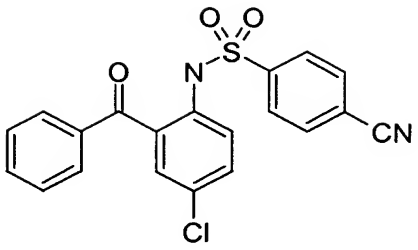

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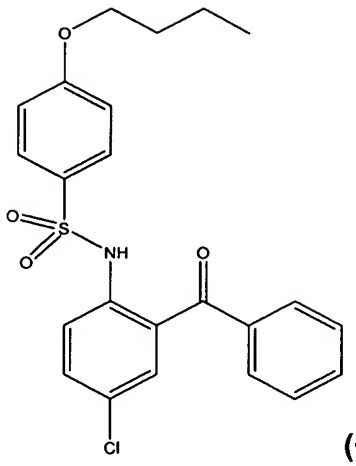
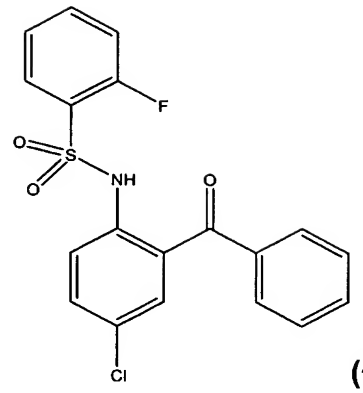
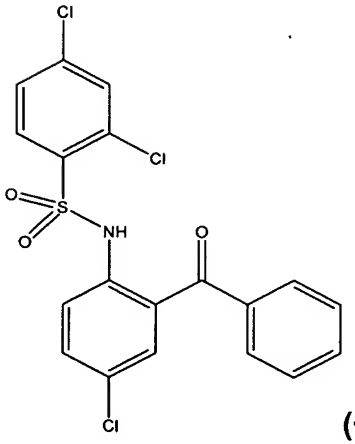
Table 3: Compounds with activity in either or both of the chemotaxis assay and calcium mobilization assays, with 1000nM < IC_{50} < 10000 nM (+):



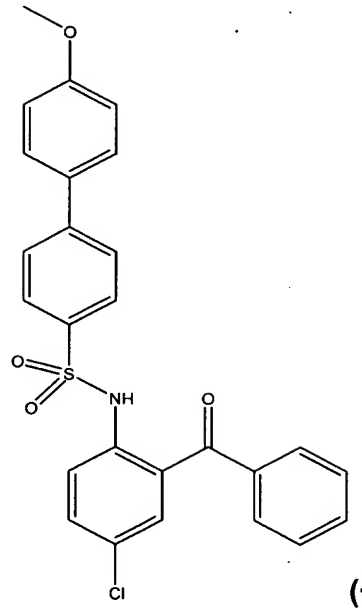
(+)



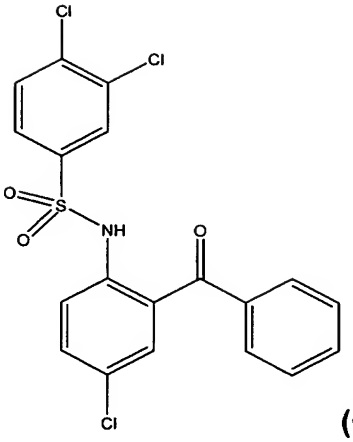
(+)



(+)



(+)



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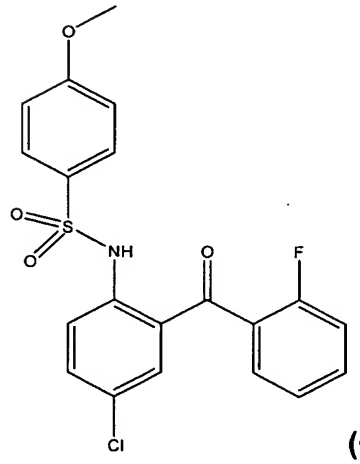

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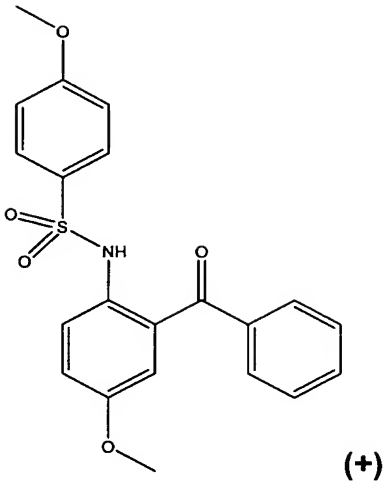

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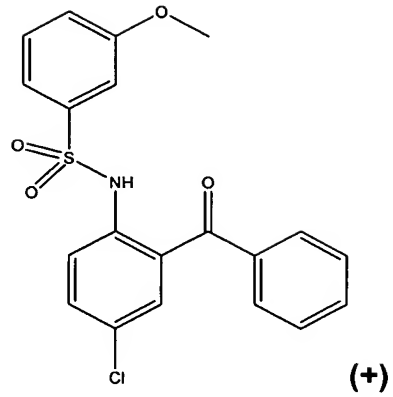

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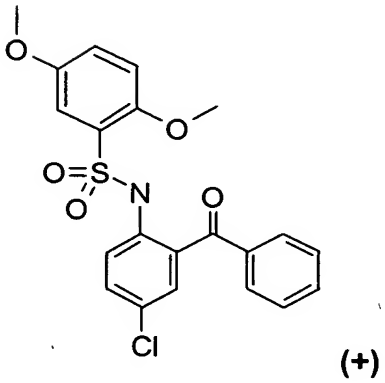

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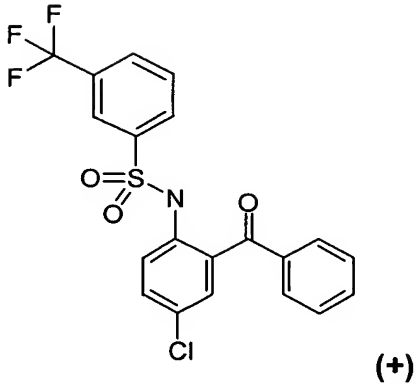

(+)

It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference for all purposes.